CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-720

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Brand Name:	Aricept®
Generic Name:	donepezil hydrochloride
Formulation:	5 and 10 mg orally disintegrating tablets (ODT)
Indication:	Treatment of Alzheimer's Disease
NDA:	21-720
Applicant:	Eisai
Submission Date:	12/18/2003 and 03/04/2004
OCPB Division:	DPE I
OND Division:	Division of Neuropharmacological Drug Products
Primary Reviewer:	Robert O. Kumi, Ph.D.
Secondary Reviewer:	Veneeta Tandon, Ph.D.

Table of Contents

I. EXECUTIVE SUMMARY

Aricept® (donepezil hydrochloride) is indicated for the treatment of Alzheimer's disease, and is available as 5 and 10 mg tablets for oral administration. The recommended dosages of Aricept are 5 mg and 10 mg once per day. In NDA 21-720, the applicant is seeking approval for new 5 and 10 mg donepezil hydrochloride orally disintegrating tablet (ODT) formulations and a manufacturing site change.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to NDA 21-720. 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, satisfactory outcome of inspection by Division of Scientific Investigations, and the applicant adequately addresses the following comments.

Comments to Applicant

1. 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.
2. 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.
3. 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.

B. Phase IV Commitments

There are no phase IV commitments.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology and biopharmaceutics program for the new 5 and 10 mg donepezil hydrochloride orally disintegrating tablets (ODT) includes two studies in which donepezil hydrochloride ODTs were given to healthy volunteers to assess bioequivalence (BE). In Study E2020-A001-015 the 10 mg donepezil hydrochloride ODT was compared to the 10 mg Aricept tablet and in Study E2020-A001-016, the proposed 5 mg ODT was compared to the Aricept 5 mg tablet. Study E2020-A001-015 was conducted at the 10 mg donepezil hydrochloride dose level and Study E2020-A001-016 was conducted at the 5 mg donepezil hydrochloride dose level. Additionally, dissolution information (data) was provided to support:

1) Setting of a dissolution specification for ODT.
2) Manufacturing site change (Eisai, Kwashima, Japan to Eisai, Misato, Japan) for ODT.

Key Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence and Dose Proportionality

- The 5 mg donepezil hydrochloride ODT is bioequivalent to the 5 mg Aricept tablet
- The 10 mg donepezil hydrochloride ODT is bioequivalent to the 10 mg Aricept tablet
- Donepezil hydrochloride exposure increased dose-proportionally from the 5 to 10 mg dose level and $t_{1/2}$ and T_{max} were comparable at the 5 and 10 mg dose levels.

Dissolution Information

- Dissolution of donepezil hydrochloride ODT in 0.1 N HCl (pH 1.1), [ ] acetate buffer (pH 4.1) and [ ] phosphate buffer containing [ ] NaOH (pH 6.8) was comparable in all three media and was rapid (over [ ] donepezil hydrochloride dissolved within 20 minutes).
- Dissolution of 5 and 10 mg donepezil hydrochloride ODT was similar at the Eisai, Kwashima, Japan and Eisai, Misato, Japan sites (f_2 for 5 mg = 89 and f_2 for 10 mg = 75).
- Overall, dissolution of donepezil hydrochloride ODT and Aricept was comparable in 0.1 N HCl, although, as expected, at earlier time points a greater amount of donepezil HCL ODT dissolved than Aricept.
  - The dissolution information support the following dissolution method and specification for the 5 mg and 10 mg ODT:

    Dissolution Method
    Dissolution medium: 0.1 N HCl, 900 mL
    USP Apparatus 2, Paddle Speed: 50 rpm

    Dissolution Specification (Interim)
    Q =[ ]% in 20 minutes

_____ Date_____
Robert O. Kumi, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation I

Concurrence:

_____ Date_____
Veneeta Tandon, Ph.D.
Acting Team Leader
Clinical Pharmacology and Biopharmaceutics
Neuropharmacological Drug Products

II. Question Based Review (QBR)

An abridged version of the Question Based Review (QBR) was employed for this review because NDA 21-720 focuses on the new 5 mg and 10 mg donepezil hydrochloride oral disintegrating tablet (ODT) formulations. For additional background information on donepezil hydrochloride, please refer to the Clinical Pharmacology and Biopharmaceutics Review for NDA 20-690.

The three main QBR topics addressed in this review are as follows:

1. General Attributes of Drug Formulation (Characteristics of 5 and 10 mg donepezil hydrochloride ODT)
2. Biopharmaceutics (Bioequivalence, Food Effect and Dissolution)
3. Analytical Section

A. What are the general attributes of the proposed 5 and 10 mg ODTs?

1. Regulatory Background

The applicant submitted the development program for "Aricept® ODT" to the Agency on 09/19/2000 and the Agency responded on 10/27/2000. The relevant clinical pharmacology and biopharmaceutics agreements reached regarding the ODT development program are as follows:

a) A bioequivalence study with 10 mg ODT can be conducted. A biowaiver could be requested for the 5 mg tablet if the two dosage strengths were proportional in composition.
b) Food effect studies were not required for the ODT tablet strengths.
c) Complete dissolution performance (dissolution profile and f_2 determinations) should be provided for 10 mg ODT (biobatch) and the 5 mg ODT and between scale ODT pilot plant batches and batches produced at selected commercial site.

2. Formulation Characteristics

The quantitative compositions of the 5 mg and 10 mg ODTs are tabulated below (Table I).

Table I: Quantitative Composition of Oral Disintegration Tablets, 5 and 10 mg

Component	Function	Quantity (mg)	
		5 mg ODT	10 mg ODT
Granule			
Donepezil hydrochloride, Eisai	Active ingredient	5	10
Mannitol, USP			
Colloidal Silicon Dioxide, NF			
Carrageenan			
Purified Water, USP			
Tablet			
Mannitol			
Polyvinyl Alcohol			
Ferric Oxide (Yellow)			
Dehydrated Alcohol			
Total Weight of ODT tablet			

As shown in Table I, the granules are proportionally similar, but the tablets are not proportionally similar. The 5 and 10 mg donepezil hydrochloride tablets are orally disintegrating

tablets and round in shape. Five and 10 mg ODT can be distinguished by color (5 mg ODT, white vs. 10 mg ODT, yellow) and embossed dose (5 vs. 10). The applicant proposed the following disintegration method and specification for ODT: USP <701>; disintegration testing performed on six tablets using USP disintegration apparatus in water at 37 ± 2^{O} C without discs. The tablets must meet the USP criteria for Uncoated tablets within 60 seconds.

3. Proposed Mechanism of Action

Donepezil HCl is postulated to exert its therapeutic effect by enhancing cholinergic function by increasing acetylcholine's (ACh) concentration. In Alzheimer's disease, there is a deficiency of cholinergic neurotransmission. Donepezil HCl is a reversible inhibitor of the enzyme cholinesterase; cholinesterase decreases ACh concentration by hydrolysis of ACh.

4. Donepezil Hydrochloride (Aricept) Dosage and Mode of Administration

The recommended dosages of Aricept are 5 mg and 10 mg once per day. The proposed dosage for the ODT is the same as the approved dosage with the following instructions: "Allow ARICEPT® ODT to dissolve on the tongue and follow with a sip of water". In the bioequivalence studies ODT tablets were placed on the tongue for approximately 10 seconds and followed by 100 mL of water; thus, it is unclear that a "sip" of water (< 100 mL) will be sufficient to ensure adequate ingestion and subsequent absorption of the formulation. The applicant did not conduct any additional clinical studies to determine if ODT would be adequately administered with a sip of water. Consequently OCPB recommends that the sip of water (suggesting a small volume of water) should not be specified in the label, rather the label should state that ODT should be taken with water (see Appendix for OCPB Labeling Revisions).

B. What are the general clinical pharmacology and biopharmaceutic highlights of donepezil?

This question did not need to be addressed for this application; please refer to NDA 20-690.

C. What intrinsic factors influence donepezil exposure and/or response?

This question did not need to be addressed for this application; please refer to NDA 20-690.

D. What extrinsic factors influence donepezil exposure and/or response?

This question did not need to be addressed for this application; please refer to NDA 20690.

E. What are the general biopharmaceutics characteristics of the 5 mg and 10 mg donepezil hydrochloride ODT formulation (Bioequivalence, Food Effect and Dissolution Characterization)?

1. Bioequivalence

The 5 and 10 mg donepezil HCl ODT are bioequivalent (BE) to the approved 5 and 10 mg Aricept tablets, respectively. BE of the 5 mg and 10 mg donepezil hydrochloride ODT to the 5 and 10 mg Aricept tablets was evaluated in studies E2020-A001-016 and E2020-A001-015,

respectively. Healthy volunteers received a single 5 or 10 mg dose of ODT and Aricept tablets on two separate occasions. Pharmacokinetic measures obtained in the studies are summarized in Table II and the 90 % confidence intervals (CIs) of the ratio (ODT/tablet) for log-transformed AUC and C_{max} are presented in Table III.

The AUC and C_{max} (exposure) increased in a dose-proportional manner over the 5 to 10 mg doses evaluated; additionally, T_{max} and half-life were similar at the 5 and 10 mg dose levels (Table II).

The 90 % CIs of the ratios (ODT/tablet) of log-transformed AUC and C_{max} are within the 80 – 125 % no-difference range, therefore the ODT donepezil HCl formulations are bioequivalent to the reference formulation.

Table II: Donepezil Mean ± SE PK Measures in Studies E2020-A001-015 and E2020-A001-016 (Healthy Volunteers)

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} (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} (h)	3.2 ± 0.2	3.3 ± 0.2
Half-life (h)	61.3 ± 4.5	62.4 ± 3.8

Table III: Donepezil HCl Bioequivalence Evaluations (ODT vs. Aricept) in Studies E2020-A001-015 and E2020-A001-016 (Healthy Volunteers)

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

2. Food

A food effect study was not requested for this application; this may have been because it was anticipated that the donepezil HCl ODT tablets would have similar food effect properties as the conventional Aricept tablets. Food does not affect the exposure of Aricept tablets. However, food affected the exposure of the new donepezil HCl [ ] (NDA 21-719): C_{max} decreased by 17 % and mean AUC was not significantly changed relative to the fasted state. The decrease in C_{max} is not considered clinically significant. Theoretically, the ODTs biopharmacuetic properties are a hybrid of the Aricept tablets and the donepezil HCl [ ] consequently, the ODT may have a

food effect that falls between the tablet (no effect) and the [ ] (non-clinically significant food effect). Overall, the available food effect information (Aricept tablet and donepezil HCl [ ] suggests that the ODT can be given with or without food.

3. Dissolution

Dissolution Method and Specification

The applicant provided sufficient dissolution information to select a dissolution method and to set a dissolution specification for donepezil HCl ODT. The proposed dissolution method for ODT is the same as that for Aricept tablets. Dissolution was evaluated using USP Apparatus II (paddle), 50 rpm, 900 mL of media at 37° C. The dissolution method development was acceptable. The media evaluated were 0.1 N HCl (pH 1.1), [ ] acetate buffer (pH 4.1) and [ ] phosphate buffer containing [ ] NaOH (pH 6.8).

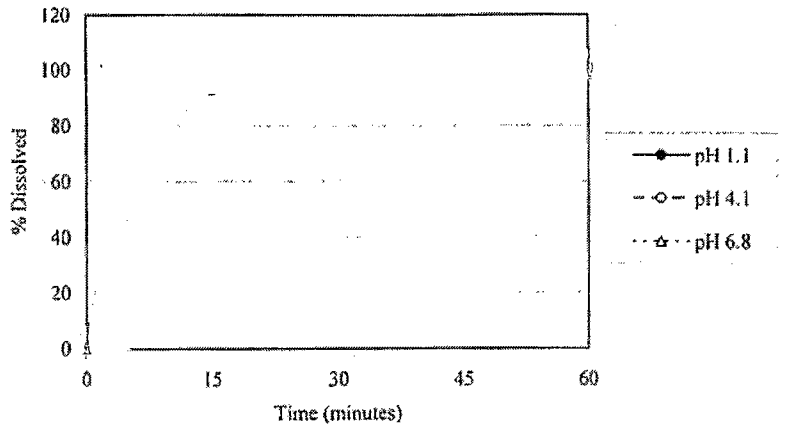


Figure 1. Dissolution Profiles for 5 mg Donepezil Hydrochloride Rapid Disintegration Tablet Obtained from Different pH Media

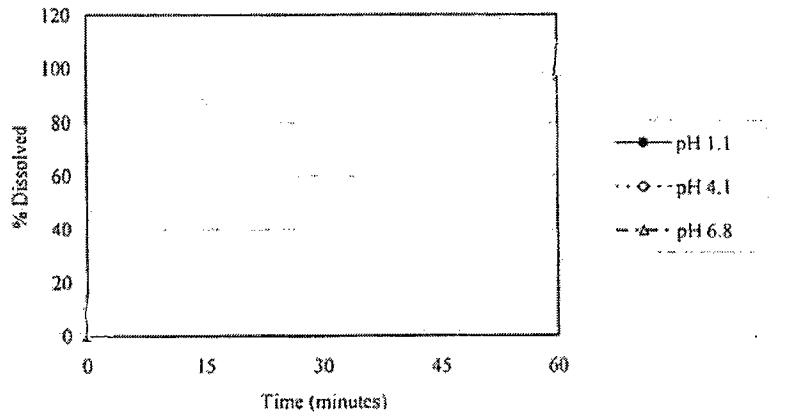
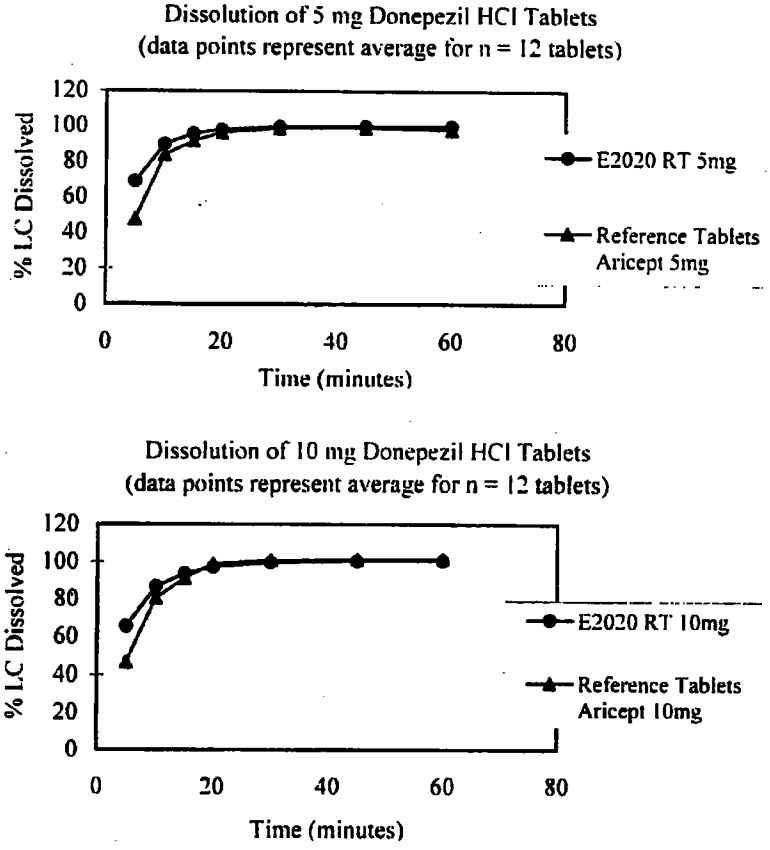


Figure 2. Dissolution Profiles for 10 mg Donepezil Hydrochloride Rapid Disintegration Tablet Obtained from Different pH Media

ODT dissolution in all evaluated media was comparable (superimposable profiles) as shown in Figures 1 and 2. The comparable dissolution in the three media indicates that any of the three media would be suitable as the dissolution medium; therefore, the applicant's choice of 0.1 N [ ] HCl is acceptable. Ideally, different paddle speeds should have been evaluated to select the final method; however, this evaluation does not appear necessary because dissolution is rapid and complete at this low paddle speed. The applicant also provided comparative dissolution data for the ODT and Aricept tablets in 0.1 N HCl that support selection of the dissolution method. As shown in figure 3, under the same dissolution conditions, dissolution profiles for ODT were comparable to those of the approved Aricept reference tablets. As expected, due to the inherent rapid disintegration of ODT, the ODT had a greater amount of donepezil HCL dissolved than the Aricept tablets at the early time points (time < 20 minutes).

Figure 3: Comparative Dissolution Profiles: ODT (E2020 RT 5 and 10 mg) vs. Aricept Tablets (5 and 10 mg)



- ***Applicant's Proposed Dissolution Method for Donepezil HCl ODT***

  USP Apparatus II (paddle)
  Dissolution medium 0.1 N HCl, 900 mL
  Paddle Speed 50 rpm

The proposed dissolution method is acceptable.

- ***Applicant's Proposed Specification*** **for donepezil HCl ODT**

  Q = [ ]% in [ ] minutes

On average, over [ ] ODT dissolved within 20 minutes with the selected dissolution method and supports the following OCPB proposed dissolution specification:

Q = [ ]% in 20 minutes

Dissolution Data Supporting Manufacturing Site Change

The 5 and 10 mg investigational formulations used in the BE studies and the proposed commercial formulations are the same. Characteristics of the investigational and commercial formulations are summarized in Table IV.

Table IV: Dissolution Information Supporting Manufacturing Site Change for donepezil HCl ODT

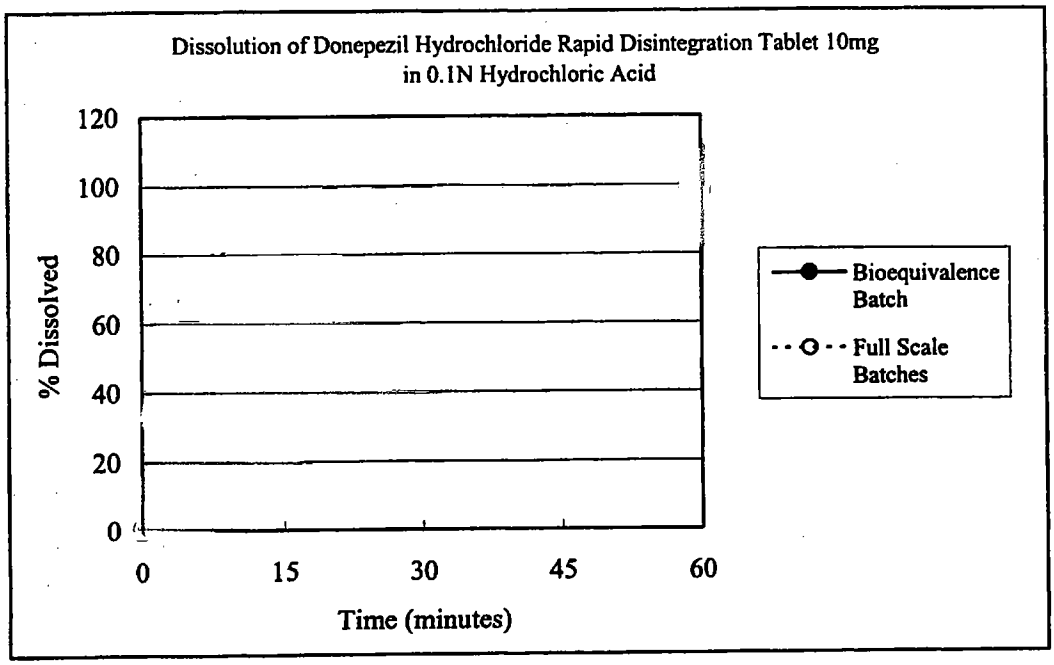
Formulation	Investigational Formulation	Commercial Formulation
Batch Size	[ ]	[ ]
Site	Kawashima, Japan	Misato, Japan
# of batches	One 5 mg and one 10 mg	Three 5 mg and three 10 mg
Dissolution Comparison	Not applicable	Dissolution profile similar to investigational formulations: f_2 = 89 for 5 mg and f_2 = 75 for 10 mg ODT Differences in percent dissolved [ ] at all time points

Please refer to Appendix under Dissolution Data for additional dissolution information.

Reviewer's Note on f_2 Calculation (Table IV)

The f_2 values may not be too meaningful because a limited number of time points met the criteria of [ ] dissolved: 5 mg tablet had [ ] dissolved at the second time point and 10 mg had [ ] [ ] at the second time point (figure 4 below). Despite the potential limitations of the f_2 calculations, it is reasonable to conclude that the products are similar because of the small differences in mean percent dissolved [ ] at all time points (Figure 4).

Figure 4: Dissolution Profiles for donepezil HCl ODT prepared on a pilot scale (BE Studies, Manufactured at Kawashima site) and in full scale batch used in BE studies and those produced on a full batch scale (Manufactured at Misato site)



F. How were donepezil concentrations measured (Bioanalytical Assay)?

A HPLC tandem MS method was used to determine donepezil hydrochloride concentrations in plasma samples. The assay performance was acceptable in both BE studies; please refer to the individual study reviews for additional details on the assay (Appendix Pg. 34 and 37).

III. Detailed Labeling Recommendations

Summary of Applicant's Proposed Labeling Changes
1. Description of new 5 and 10 mg ODT

2. Clinical Pharmacokinetics Section
Food effect Information: Statement added to indicate that food does not alter donepezil exposure with donepezil HCl tablets (ODT and conventional).

3. Dosage and Administration Section
Include statement indicating that ODT should be allowed to dissolve on tongue and followed with sip of water.

OCPB Labeling Recommendations: Labeling Revisions to Proposed Labeling Changes
In general, the applicant's labeling comments are acceptable. The following comments should be conveyed to the applicant.

1. Information for all donepezil HCl formulations should be in one label. To facilitate this merging of labels the following should be addressed:
   a) Clinical Pharmacokinetics Section:
      i. Provide bioequivalence information for ODT
      ii. Include a statement indicating that a food effect study was not conducted with ODT; however, the effect of food with ODT is expected to be minimal.
   b) Dosage and Administration Section
      i. Change mode of administration of ODT: after ODT dissolves on tongue follow with water

APPENDIX

21 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS STUDY REVIEW

Study: E2020-A001-015

Title: A bioavailability/bioequivalence study of 10 mg donepezil hydrochloride rapid disintegration tablet compared to a reference tablet in healthy volunteers

Investigators: [

Site:]

Study Period: 12/26/2000- 02/26/2001

Objectives: To assess the bioavailability/bioequivalence of 10 mg donepezil hydrochloride rapid disintegration tablets relative to a reference donepezil hydrochloride tablet

Reviewer Note

The FDA does not accept the rapid disintegration tablet (RDT) terminology because the term "rapid" may be misleading (may suggest rapid onset of action); therefore, the FDA refers to these dosage forms as orally disintegrating tablets or ODT. The ODT terminology will be adopted for the remainder of this review.

Study Design:

An open label, randomized, two period, two sequence, crossover study design was employed. During each treatment period, healthy adult volunteers received a single oral dose of 10 mg donepezil hydrochloride, either as a 10 mg ODT or conventional tablet (Aricept®). The ODT was placed on the tongue for ~ 10 s and followed by 100 mL of water. Each treatment period was approximately 10 days in duration and separated by a 14-day wash out period. Standard dietary restrictions with respect to food (fasted) and fluid (100 mL water) consumption were followed.

Selected Demographic Characteristics of Subjects who Completed the Study (n = 20):

- Gender : 14 male and 6 female
- Age: Mean (SE) 35.7 (1.6) years; range 20 – 45 years
- Race : 20 Hispanic
- Weight: Mean (SE) 73.5 (1.6) kg, Range: 61.8 – 85.9 kg

Sample Collection

Blood samples were collected at –1 hr (predose) and 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hr postdose.

Analytical Methodology:

A validated LC/MS/MS method was used to determine donepezil concentrations in plasma; assay performance was acceptable with the following characteristics.

Table I: Assay* Performance and Acceptability- Donepezil Plasma Samples

Criterion	Observation	Comment
Linearity	Standard Curve was linear over 0.20 – 60.0 ng/mL range with $R^2 \geq 0.9993$	Satisfactory
Accuracy	Percent difference from theoretical concentration of QC samples ≤ 5 %	Satisfactory
Precision	Coefficient of variation of QC samples < 6 %	Satisfactory
Specificity	Sample chromatograms indicated that interference does not occur	Satisfactory

*Assay conducted by [ ]

The concentrations (ng/mL) of the QC samples were: QC1 = 0.6, QC2 = 4.0 QC3 = 40.0.

Formulations

- **Reference**: Film coated donepezil hydrochloride 10.0 mg tablet (Aricept®), Batch #10AR0124, manufactured by Eisai Inc., Research Triangle Park, NC, US.
- **Test:** Orally disintegrating tablet formulation of donepezil hydrochloride 10.0 mg, Lot #0YZ06P, manufactured by Eisai, Kawashima, Japan.

Pharmacokinetic Analysis

Noncompartmental methods were used to estimate donepezil PK measures: C_{max}, T_{max}, AUC_{∞}, and $t_{1/2}$.

Statistical Analysis

Standard pharmacokinetic-statistical analyses were used to evaluate bioequivalence between the two formulations. The two products were considered bioequivalent if the 90 % CI for the geometric mean ratio (test/reference) for both AUC and C_{max} were entirely contained between 0.80 and 1.25 .

I. RESULTS AND DISCUSSION

Subject Disposition

Twenty-two subjects enrolled in the study, but only 18 subjects were included in the PK analysis. Two subjects discontinued from the study due to adverse events. The other two subjects completed the study but were excluded from the PK analysis because they did not have detectable concentrations in Period 2 or vomited 9 hours post dose.

Reviewer Note on Data Exclusion

Exclusion of the subject who did not have detectable concentrations is reasonable because subject may not have swallowed the tablet. However, exclusion of data from the subject who vomited at 9 hr post-dose is debatable because 9 hr is outside the 2 x T_{max} window specified in the *Guidance for Industry*: Bioequivalence and Bioavailability Studies for Orally Administered Drug Products.

A. Pharmacokinetics

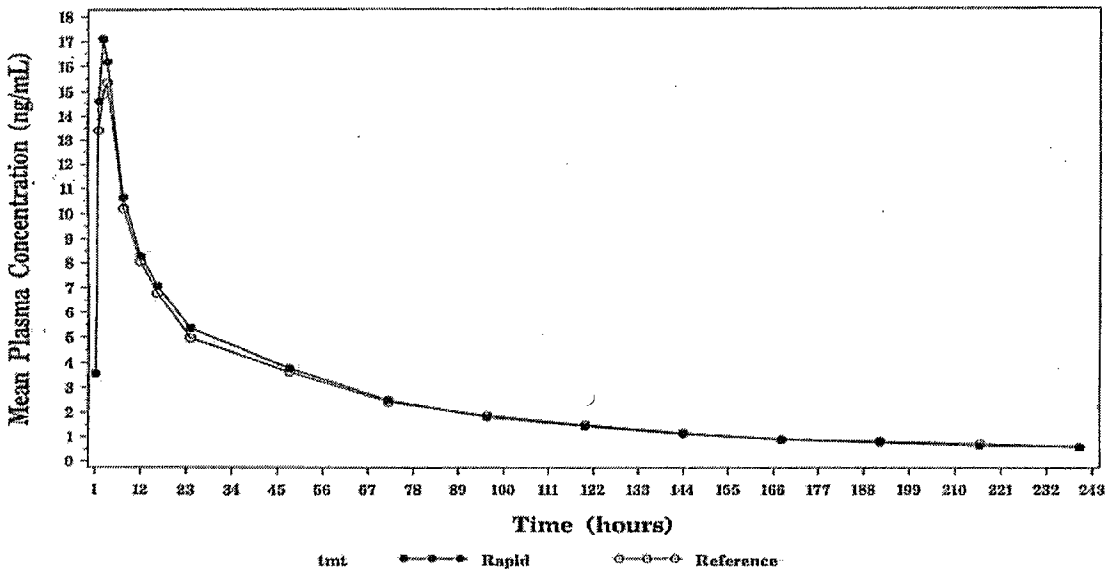
The mean plasma concentration-time profiles are depicted in Figure 1 and Pharmacokinetic data for the two treatment groups are summarized in Table II.

Table II: Donepezil Mean ± SE Measures in Healthy Volunteers (n = 18)

Parameter	Single Dose Treatments 10 mg donepezil hydrochloride Formulations	
	ODT (Test)	Tablet (Reference)
$AUC_{0\text{-}240}$ (ng·h/mL)	615 ± 57	647 ± 66
C_{max} (ng/mL)	17.7 ± 1.0	17.3 ± 0.8
T_{max} (h)	3.11 ± 0.18	3.333 ± 0.31
Half-life (h)	61.6 ± 3.8	64.35 ± 5.1

The 90 % CIs of the ratio ([redacted]/tablet) for log-transformed AUC and C_{max} are within the 80 – 125 % no-difference range, therefore the ODT donepezil HCl formulation is bioequivalent to the reference formulation.

Figure* 1: Mean donepezil plasma concentration-time in healthy volunteers (study E2020-A001-015) receiving single 10 mg donepezil hydrochloride dose as ODT or tablet (fasted state)



*** In figure rapid refers to ODT and reference refers to Aricept tablet**

Table III: Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Mean AUC and C_{max} Ratios (ODT/tablet)

PK Measure	90 % CI
C_{max} (ng/mL)	100.30 – 107.40
AUC_{0-240} (ng·h/mL)	93.79 – 103.54

Safety Results (Applicant's Conclusions)

No significant safety issues were associated with the 10 mg donepezil HCl ODT formulation relative to the reference 10 mg Aricept tablet formulation. No deaths or other serious adverse events were reported during the study. Please refer to the Clinical Review for additional safety information.

CONCLUSION

The 10 mg ODT donepezil HCL formulation is bioequivalent to the 10 mg tablet donepezil HCL (Aricept) reference formulation.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS STUDY REVIEW

Study: E2020-A001-016

Title: A bioavailability/bioequivalence study of 5 mg donepezil hydrochloride rapid disintegration tablet compared to a reference tablet in healthy volunteers

Investigators: [redacted]

Site: [redacted]

Study Period: 12/26/00 - 03/06/01

Objectives: To assess the bioavailability/bioequivalence of 5 mg donepezil hydrochloride rapid disintegration tablets relative to a reference donepezil hydrochloride tablet

Study Design:

An open label, randomized, two period, two sequence, 2-way crossover study design was employed. During each treatment period, healthy adult volunteers received a single oral dose of 5 mg donepezil hydrochloride, either as a 5 mg rapidly disintegrating tablet (RDT) or 5 mg conventional tablet form. The ODT was placed on the tongue for ~ 10 s and followed by 100 mL of water. Each treatment period was approximately 10 days in duration and separated by a 14-day wash out period. Standard dietary restrictions with respect to food (fasted) and fluid (100 mL water) consumption were followed.

Reviewer Note

The FDA does not accept the rapid disintegration tablet (RDT) terminology because the term "rapid" may be misleading (may suggest rapid onset of action); therefore, the FDA refers to these dosage forms as orally disintegrating tablets or ODT. The ODT terminology will be adopted for the remainder of this review.

Selected Demographic Characteristics of Subjects who Completed the Study (n = 20)

- Gender : 9 male, 11 female
- Age: Mean (SE) 31.4 (1.4) years; range 23 – 44 years
- Race: 19 Hispanic, 1 White
- Weight: Mean (SE) 69.6 (1.1) kg, Range: 60.0 - 76.8 kg

Sample Collection

Blood samples were collected at –1 hr (predose) and 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hr postdose.

Analytical Methodology:

A validated LC/MS/MS method was used to determine donepezil concentrations in plasma samples; assay performance was acceptable with the following characteristics.

Table I: Assay Performance and Acceptability- Plasma Samples

Criterion	Observation	Comment
Linearity	Standard Curve was linear over the 0.20 – 60.0 ng/mL range with $R^2 \geq 0.9997$	Satisfactory
Accuracy	Percent difference from theoretical concentration of QC samples ≤ 5 %	Satisfactory
Precision	Coefficient of variation of QC samples < 6 %	Satisfactory
Specificity	Sample chromatograms indicated that interference does not occur	Satisfactory

*Assay conducted by [redacted]

The concentrations (ng/mL) of the QC samples were: QC1 = 0.6, QC2 = 4.0 QC3 = 40.0.

Formulations

- **Reference** Film coated donepezil hydrochloride 5.0 mg tablet (Aricept®), batch number 05AR0085, manufactured by Eisai Inc., Research Triangle Park, NC, US.
- **Test** Orally disintegrating tablet formulation of donepezil hydrochloride 5.0 mg; lot number 0YZ05P, manufactured by Eisai, Kawashima, Japan.

Pharmacokinetic Analysis

Noncompartmental methods were used to estimate donepezil PK measures: C_{max}, T_{max}, AUC_{∞} and $t_{1/2}$.

Statistical Analysis

Standard pharmacokinetic-statistical analyses were used to evaluate bioequivalence between the two formulations. The two products were considered bioequivalent if the 90 % CI for the geometric mean ratio (test/reference) for both AUC and C_{max} were entirely contained between 0.80 and 1.25 .

II. RESULTS AND DISCUSSION

Subject Disposition

All enrolled subjects completed the study; however, data from one subject (Subject 11) were excluded from the PK analysis because his donepezil plasma levels were not detectable during Period 2. Exclusion of these data is acceptable.

A. Pharmacokinetics

The mean donepezil plasma concentration-time profiles are depicted in Figure 1 and pharmacokinetic data for the two treatment groups are summarized in Table II.

Figure 1: Mean Donepezil Plasma concentration-time in Healthy Volunteers (Study E2020-A001-016) Receiving single 5 mg Donepezil Hydrochloride Dose as ODT and Tablet (fasted state)

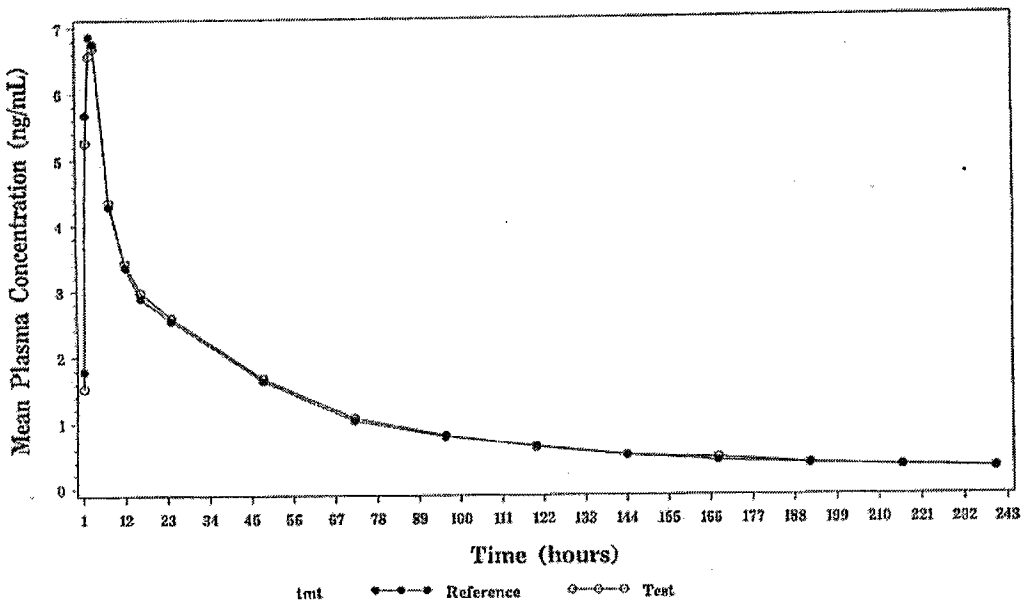


Table II: Donepezil Mean ± SE Measures in Healthy Volunteers (n = 19)

Parameter	Single Dose Treatments 5 mg donepezil Formulations	
	ODT (Test)	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} (h)	3.2 ± 0.2	3.3 ± 0.2
Half-life (h)	61.3 ± 4.5	62.4 ± 3.8

The 90 % CIs of the ratio (ODT/tablet) for AUC and C_{max} are within the 80 – 125 % no-difference range, therefore the ODT donepezil HCl formulation is bioequivalent to the reference formulation.

Table III: Ninety Percent (90 %) Confidence Intervals (CI) of Log Transformed Mean AUC and C_{max} Ratios (ODT/tablet)

PK Measure	90 % CI
C_{max} (ng/mL)	93.95 – 105.76
AUC_{0-240} (ng·h/mL)	92.65 – 104.81

B. Safety Results (Applicant's Conclusions)

No significant safety issues were associated with the 5 mg ODT formulation relative to the reference 5 mg Aricept tablet formulation. No deaths or other serious adverse events were reported during the study. Please refer to the Clinical Review for additional safety information.

C. CONCLUSION

The 5 mg donepezil HCL ODT formulation is bioequivalent to the 5 mg Aricept reference tablet formulation.

DISSOLUTION INFORMATION (DATA and Profiles)

5 mg Tablet Individual Dissolution Values

Lot : P0529902A

Vessel	Time (minutes) 5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	68.7	89.6	95.7	97.8	99.5	99.9	99.9
min.(%)							
max.(%)							
RSD	10.00	3.57	2.14	1.95	1.97	1.97	1.88

Lot : Misato: 24C39M

Vessel	Time (minutes) 5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	72.4	93.4	98.9	101.1	102.4	102.7	103.0
min.(%)							
max.(%							
RSD	9.23	2.44	0.91	0.96	1.00	1.02	0.74

Lot : Misato: 24C43M

Vessel	Time (minutes) 5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	68.9	91.8	97.6	99.4	100.5	100.9	101.0
min.(%)							
max.(%)							
RSD	11.31	2.84	1.48	1.50	1.54	1.64	1.56

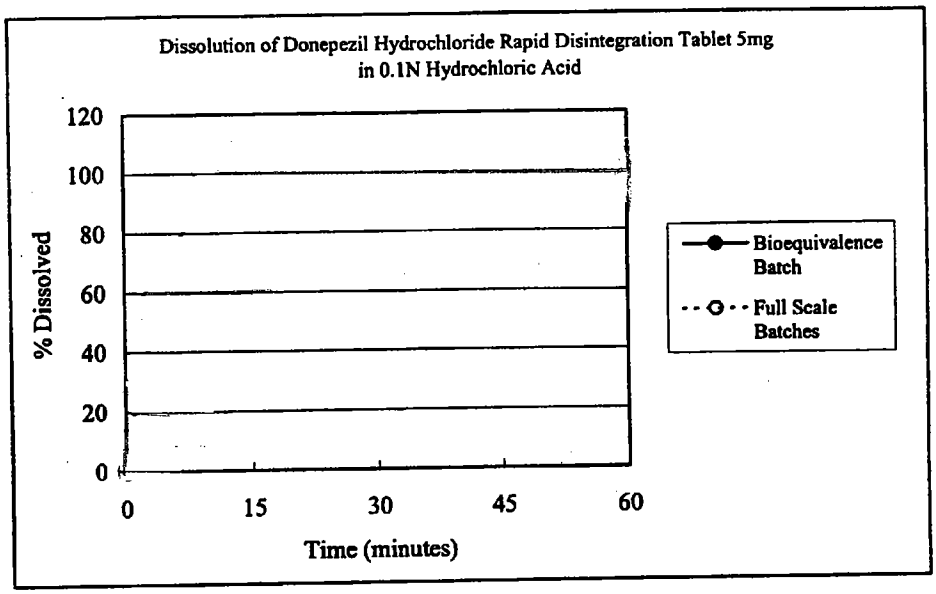
Lot : Misato: 25C92M

Vessel	Time (minutes) 5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	63.0	88.0	95.5	98.0	99.2	99.3	99.5
min.(%)							
max.(%)							
RSD	7.48	2.39	1.10	1.01	1.10	1.06	1.08

Table 7-4. Average Percent Dissolved for Donepezil Hydrochloride Rapid Disintegration Tablets, 5 mg, Bioequivalence Batch and ECL-Misato Full Scale Batches

Time (Minutes)	Average Percent Dissolved					Percent Difference
	ECL-Misato PQ Batch Numbers				ECL-Kawashima Bioequivalence Batch	|Biobatch – Full Scale Batch $_{Avg}$|
	24C39M	24C43M	25C92M	Average	P0529902A	
5						
10						
15						
20						
30						
45						
60						
f_2				89		

Figure 7-1. Dissolution Profile Comparison of Donepezil Hydrochloride Rapid Disintegration Tablets, 5 mg biobatch versus ECL-Misato (3 Full Scale Batch Average).



10 mg Tablet Individual Dissolution Values

Lot : P0529902B

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1	60.0	84.6	92.0	95.0	97.3	98.3	98.8
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	62.3	84.9	93.1	97.0	100.4	102.0	102.8
min.(%)							8
max.(%)							
RSD	13.25	5.17	3.33	2.90	3.11	3.54	3.96

Lot : Misato: 25C18M

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	64.7	86.8	92.6	94.4	95.5	95.5	94.7
min.(%)							
max.(%)							
RSD	11.20	3.76	2.01	1.89	2.01	2.14	2.14

Lot : Misato: 25C19M

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	70.3	88.9	94.6	97.0	99.1	100.0	100.3
min.(%)							
max.(%)							
RSD	9.09	1.87	1.47	1.42	1.36	1.42	1.47

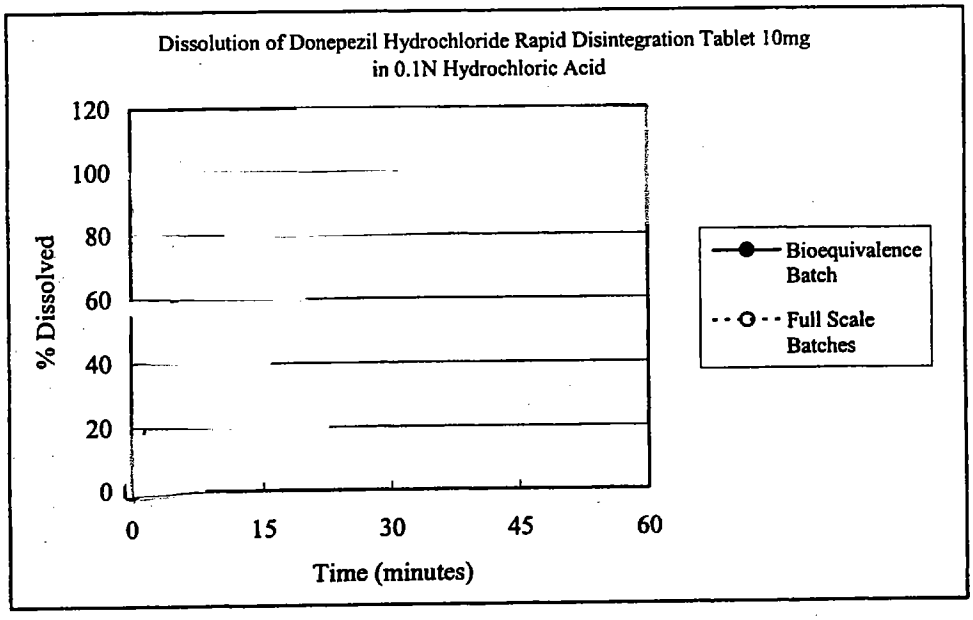
Lot : Misato: 25C89M

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
avg.(%)	64.1	86.8	94.1	97.1	99.3	100.2	100.3
min.(%)							
max.(%)							
RSD	12.40	4.11	1.73	1.48	1.56	1.62	1.69

Table 7-5. Average Percent Dissolved for Donepezil Hydrochloride Rapid Disintegration Tablets, 10 mg, Bioequivalence Batch and ECL-Misato Full Scale Batches

Time (Minutes)	Average Percent Dissolved					Percent Difference
	ECL-Misato PQ Batch Numbers				ECL-Kawashima Bioequivalence Batch	|Biobatch – Full Scale Batch $_{Avg}$|
	25C18M	25C19M	25C89M	Average	P0529902B	
5						
10						
15						
20						
30						
45						
60						
f_2				75		

Figure 7-2. Dissolution Profile Comparison of Donepezil Hydrochloride Rapid Disintegration Tablets, 10 mg biobatch versus ECL-Misato (3 Full Scale Batch Average).



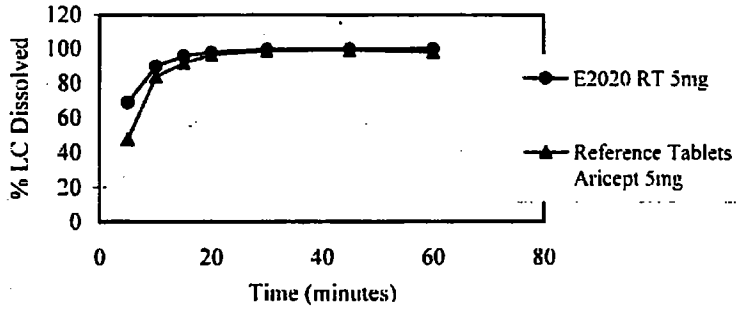
Dissolution Comparison for 5 mg Donepezil Hydrochloride Tablets

	Time (min)	%Label Claim Dissolved 5	10	15	20	30	45	60
RT 5mg P0529902A	Hydrochloric Acid (n=12 tablets)							
	average	69	90	96	98	100	100	100
	% RSD	10.0	3.6	2.1	2.0	2.0	2.0	1.9
Reference 05AR0085	average	47	84	91	96	99	99	98
	% RSD	17.4	23.9	12.8	9.5	6.2	4.1	2.2

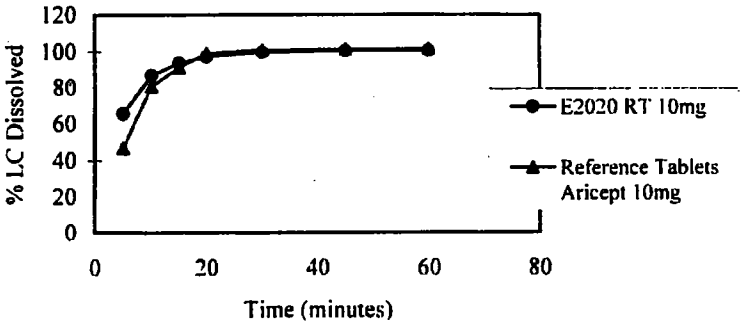
Dissolution Comparison for 10 mg Donepezil Hydrochloride Tablets

	Time (min)	%Label Claim Dissolved 5	10	15	20	30	45	60
RT 10mg P0529902B	Hydrochloric Acid (n=12 tablets)							
	average	65	87	94	97	100	100	101
	% RSD	13.3	3.8	1.8	1.5	1.3	1.5	1.5
Reference 10AR0124	average	47	81	91	99	101	101	102
	% RSD	9.6	12.0	7.8	0.1	0.5	0.1	0.1

Dissolution of 5 mg Donepezil HCl Tablets
(data points represent average for n = 12 tablets)



Dissolution of 10 mg Donepezil HCl Tablets
(data points represent average for n = 12 tablets)



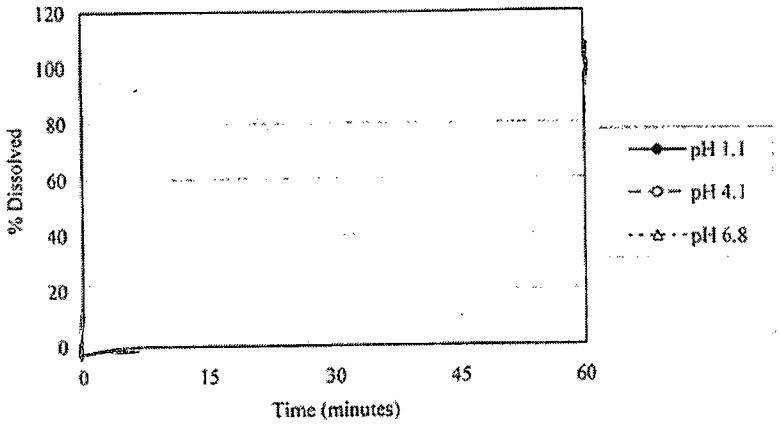


Figure 1. Dissolution Profiles for 5 mg Donepezil Hydrochloride Rapid Disintegration Tablet Obtained from Different pH Media

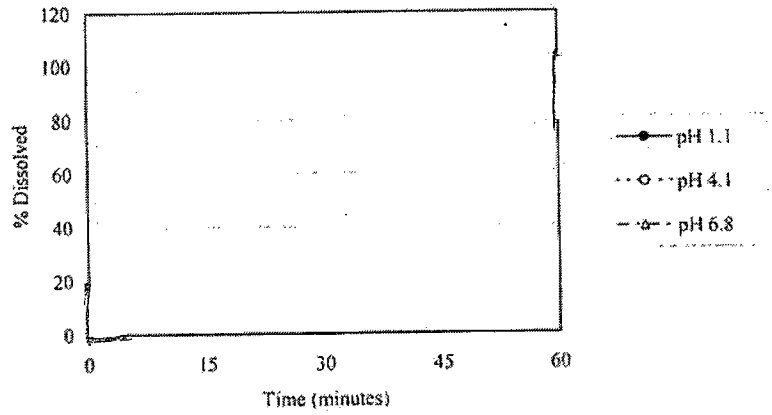


Figure 2. Dissolution Profiles for 10 mg Donepezil Hydrochloride Rapid Disintegration Tablet Obtained from Different pH Media

Donepezil hydrochloride rapid disintegration tablet 10 mg, lot P0529902B

Dissolution medium: Hydrochloric acid (pH1.1)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	65.4	86.7	93.7	97.0	99.5	100.4	100.5
Min.(%)							
Max.(%)							
RSD (%)	13.31	3.76	1.79	1.53	1.31	1.47	1.53

Dissolution medium: Acetate buffer (pH4.1)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	69.5	85.4	91.6	97.0	99.3	99.3	100.8
Min.(%)							
Max.(%)							
RSD (%)	5.96	1.93	1.21	1.24	1.13	1.26	1.31

Dissolution medium: Phosphate buffer containing . sodium hydroxide (pH6.8)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	70.4	89.9	95.4	97.7	99.1	99.4	99.5
Min.(%)							
Max.(%)							
RSD (%)	9.54	1.73	1.18	1.22	1.15	1.21	1.39

Donepezil hydrochloride rapid disintegration tablet 5 mg, lot P0529902A

Dissolution medium: Hydrochloric acid (pH1.1)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	68.7	89.6	95.7	97.8	99.5	99.9	99.9
Min.(%)							
Max.(%)							
RSD (%)	10.00	3.57	2.14	1.95	1.97	1.97	1.88

Dissolution medium: Acetate buffer (pH4.1)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	71.8	87.7	93.2	97.8	99.3	100.2	101.0
Min.(%)							
Max.(%)							
RSD (%)	7.53	2.78	1.42	1.20	1.21	1.09	1.14

Dissolution medium: Phosphate buffer containing sodium hydroxide (pH6.8)

	Time (minutes)						
Vessel	5	10	15	20	30	45	60
#1							
#2							
#3							
#4							
#5							
#6							
#7							
#8							
#9							
#10							
#11							
#12							
Avg.(%)	69.7	90.1	96.1	98.3	99.7	99.7	99.4
Min.(%)							
Max.(%)							
RSD (%)	10.46	3.08	1.84	1.86	1.71	1.37	1.35

Office of Clinical Pharmacology and Biopharmaceutics ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	21-720	**Brand Name**	Aricept
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Donepezil hydrochloride
Medical Division	HFD-120	**Drug Class**	Reversible inhibitor of acetylcholinesterase
OCPB Reviewer	Robert O. Kumi, Ph.D.	**Indication(s)**	Treatment of mild to moderate dementia of the Alzheimer's type
OCPB Team Leader	Ramana Uppoor, Ph.D.	**Dosage Form**	Rapidly disintegrating tablets (RDT), 5 and 10 mg
		Dosing Regimen	5 or 10 mg once daily with or without food
Date of Submission	12/18/2003	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	7/18/2004	**Applicant**	Eisai
PDUFA Due Date	10/18/2004	**Priority Classification**	Standard
Division Due Date	9/18/2004		

Clinical Pharmacology and Biopharmaceutics Information

Background

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase. Aricept® (donepezil hydrochloride) Tablet, approved in NDA 20-690 (11/25/1996), is indicated for the treatment of patients with mild to moderate Alzheimer's dementia. The recommended Aricept doses are 5 or 10 mg once daily with or without food.

What is the purpose of the current submission (NDA 21-720)

The applicant seeks approval of a new rapidly disintegrating Aricept® tablet in NDA 21-720.

Regulatory Background

NDA 21-720: Aricept® RDT, 5 and 10 mg (donepezil hydrochloride rapidly disintegrating tablets)
The applicant submitted the development program for Aricept ® RDT to the Agency on 09/19/2000 and the Agency responded on 10/27/2000. The relevant clinical pharmacology and biopharmaceutic agreements reached regarding the RDT development program are as follows:

d) A bioequivalence study with 10 mg RDT can be conducted. A biowaiver could be requested for the 5 mg tablet if the two dosage strengths were proportional in composition.
e) Food effect studies were not required for the RDT tablet strengths
f) Complete dissolution performance (dissolution profile and f_2 determinations) should be provided for 10 mg RDT (biobatch) and the 5 mg RDT and between scale RDT pilot plant batches and batches produced at selected commercial site.

Information submitted in application

1) NDA 21-720: Aricept® RDT

The NDA 21-720 application provides data from two studies: E2020-A001-015 (Study 015) and E2020-A001-016 (Study 016). Study 015 is a bioequivalence (BE) study with the 10 mg tablet and Study 016 is a BE study with the 5 mg tablet. The applicant also included information from European and Japanese BE studies as supportive safety information. The applicant provided dissolution data as requested.

Labeling Proposals

- Add wording to the Description section regarding the new formulations
- Add wording in the Dosage and Administration section as to how formulation should be taken (dissolve on tongue and follow with a sip of water)
- Add product descriptions to How Supplied Section

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-	-	-	

multiple dose:	-	-	-	
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	-	
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	-	-	-	
Dissolution:	-	-		
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		2	2	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		**Please forward to applicant :** 1. Please provide an additional set of review volumes for the CMC section. 2. Please provide the dissolution method development report for Aricept rapidly disintegrating tablets. This report should include dissolution in three dissolution media (different pH). If this data is already submitted, please indicate the location and provide a desk copy of the volume. 3. To facilitate the review process, please provide the following dissolution data in an electronic format: a) data from the bioequivalence batches b) data from the full scale batches
Comment to Project Manager	Please request a DSI inspection for the following study: *Study E2020-A001-015* **Investigators:** [redacted] **Site:** **Study Period:** 12/26/2000- 02/26/2001 **Title:** A Bioavailability/Bioequivalence Study of 10 mg Donepezil Hydrochloride Rapid Disintegration Tablet Compared to a Reference Tablet in Healthy Volunteers	
QBR questions (key issues to be considered)	1) Does the exposure information (relative bioavailability/bioequivalence studies) support approval of the proposed RDT tablets? 2) Does one expect a different food effect on Aricept RDT compared to conventional (approved) Aricept tablets?	
Other comments or information not included above	1. The applicant provided a separate label for the RDT Aricept formulation; however, consideration should be made to combine labeling information on the proposed Aricept RDT with approved Aricept tablets.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-720, HFD-850(Electronic Entry or Lee), HFD-120(Griffis, HFD-860 (R. Uppoor, A. Rahman, M. Mehta)

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

/s/

Robert Kumi
7/1/04 04:19:23 PM
BIOPHARMACEUTICS

Veneeta Tandon
7/1/04 04:24:42 PM
BIOPHARMACEUTICS