DEMENTIA TIMES

Newsletter – Issue 11

In this issue

Welcome note

Welcome to *Dementia Times,* a newsletter which features updates from latest research published in peer-reviewed journals with independent commentaries from key experts in the region in the field of dementia.

In the absence of disease-modifying drugs for Alzheimer's disease (AD), preventing or delaying disease progression becomes an important strategy in reducing the incidence of AD and dementia. Identifying individuals with mild cognitive impairment (MCI) who are at higher risk of progression to dementia is key to this approach.

In this issue, we will look at indicators and predictors of progression to dementia. We first evaluate the role of executive dysfunction as an indicator of progression, followed by a study which examines features that can predict the rate of cognitive decline in individuals with MCI. Lastly, we explore the utility of both magnetic resonance imaging (MRI) markers and cognitive scores as a tool to predict onset of dementia in individuals with MCI.

We hope you find these articles interesting and look forward to any feedback.

– Editors

Prof. Ming-Chyi Pai

Professor, Department of Neurology;
Director, Institute of Gerontology,
Medical College and Hospital,
National Cheng Kung University, Taiwan

Prof. So Yeon Jeon

Clinical Professor,
Department of Psychiatry,
Chungnam National University Hospital,
South Korea

Dr. Chi-Leung Lam

Director,
The Medical Centre for Cognition and Emotion (HK),
Hong Kong

Abbreviations in this issue

ACS: Alzheimer's clinical syndrome; AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADNI: Alzheimer's Disease Neuroimaging Initiative; aMCI: amnestic mild cognitive impairment; AUC: area under the receiver operating curve; CDR-SB: Clinical Dementia Rating-Sum of Boxes; GDS: Geriatric Depression Scale; maMCI: multidomain amnestic mild cognitive impairment; MCI: mild cognitive impairment; MMSE: Mini–Mental State Examination; MRI: magnetic resonance imaging; naMCI: non-amnestic mild cognitive impairment; NPI-Q: Neuropsychiatric Inventory Questionnaire; sMCI: single domain amnestic mild cognitive impairment; SNIPE: Scores by Nonlocal Image Patch Estimator; WAIS: Wechsler Adult Intelligence Scale.

Role of executive functions in the conversion from mild cognitive impairment to dementia

Authors: Junquera A, *et al.*

INTRODUCTION

Executive functions are impaired in individuals with MCI, with data suggesting that those with MCI with executive dysfunction (dysexecutive MCI) seem to decline faster than those with amnestic MCI (aMCI). Additionally, longitudinal studies found that multidomain amnestic MCI (maMCI) involving memory and executive functions exhibits the fastest progression to dementia in Alzheimer's clinical syndrome (ACS). As such, the impairment of executive function may be a promising phenotype of MCI linked to the risk of dementia in ACS. The objective of this longitudinal study was to analyze the role of executive functions in predicting the conversion of MCI to dementia in individuals with ACS.

METHODS

The study included 51 cognitively unimpaired participants and 94 participants with MCI (n=145) recruited from different hospitals and senior centres in Madrid, Spain. Participants with MCI were initially classified using the traditional, memory-based MCI classification – single domain amnestic (sMCI), maMCI and non-amnestic (naMCI).

Tests assessing executive functions, cognitive screening and instrumental activities of daily living measures were administered at baseline and at 1-year follow-up. Neuropsychological battery assessment used included screening test (Mini-Mental State Examination [MMSE]) and functional and clinical scales (Lawton & Brody; ECOG scale; Blessed scale; Clinical Dementia Rating (CDR); and Neuropsychiatric Inventory Questionnaire (NPI-Q). Cognitive domain measures included memory (Verbal Learning Test España-Complutense; Rey Osterrieth Complex Figure test), language (Boston Naming Test), visuo-spatial ability (Rey Osterrieth Complex Figure test), attention (digits [WAIS-IV]) and executive functions (WAIS-IV; Trail-Making Test; Stroop Test; Verbal Fluency – phonemic and categories; Zoo Map).

K-mean cluster analysis was performed to identify clusters of MCI patients based on executive functions variables. Linear and stepwise regression analyses were employed to assess the accuracy of executive functioning-based classification in predicting progression to dementia 1 year later.

RESULTS

Cluster analysis based on executive function among participants with MCI identified 3 clusters of dysexecutive MCI:

- Cluster 1 (n=56) exhibited the most heterogeneous mixture of sMCI, maMCI and naMCI
- Cluster 2 (n=28) consisted of mainly maMCI and naMCI
- Cluster 3 (n=10) included maMCI only.

Table 1 presents the distribution of participants who progressed to dementia in the ACS within a year. Based on the classical memory-based MCI classification, only participants with maMCI progressed to dementia in the ACS within a year (10/48 participants). Importantly, these participants were part of Cluster 3 only (10/10 patients). This suggests that MCI-dementia progression is more likely to occur in the maMCI category, and the dysexecutive MCI classification is more accurate in predicting progression to dementia in the ACS within a year compared with the classical memory-based MCI classification.

	MCI			Clusters		
	s	ma	na	1	2	3
N total	22	48	15	57	28	10
N converted	0	10	0	0	0	10
% conversion	0	**20.83%**	0	0	0	**100%**

Table 1. Distribution of study participants who progressed to dementia in ACS a year later according to the traditional memory-based MCI classification and clusters based on executive dysfunction. Abbreviations: s, single domain amnestic; ACS, Alzheimer's clinical syndrome; ma, multidomain amnestic; MCI, mild cognitive impairment; na, non-amnestic.

Dysexecutive MCI classification predicted 63% of the variance of the conversion to dementia **(Table 2),** even after controlling for severity of the disease at baseline, whereas the classical memory-based MCI classification failed to predict MCI-dementia conversion. Additional stepwise linear regression analysis found that dysexecutive classification and Category Fluency are best predictors which significantly accounted for conversion to dementia in ACS **(Table 2).** Furthermore, Trail-Making Test B/A and Verbal Fluency–Categories were able to account for 45% of variance associated to MCI-dementia progression in ACS **(Table 2),** suggesting that 'switching' and categories verbal fluency were components of executive functions that can better predict MCI conversion to dementia in ACS within a year.

	F	Sig.	R^2
TMTB-A	48.052	0.000	0.414
TMTB-A + Fluency Semantic Categories	27.489	0.000	0.451

	F	Sig.	R^2
Classical MCI	0.082	0.776	0.001
Dysexecutive MCI	41.917	0.000	0.381
Classical MCI + MMSE	5.090	0.955	0.070
Dysexecutive MCI + MMSE	116.251	0.000	0.631

	F	Sig.	R^2
Dysexecutive MCI	116.251	0.000	0.631
Dysexecutive MCI + Category Fluency	62.934	0.000	0.653

Table 2. Linear regression models assessing predictors of conversion to dementia in ACS. Abbreviations: MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; Sig, significance; TMTB-A, Trail-Making Test B/A.

CONCLUSION

Worse performance on executive function tasks in maMCI contributes to a higher risk of MCI-dementia conversion in ACS, highlighting the important role of executive function as an early predictor of dementia in ACS. Switching abilities and verbal fluency (categories) should be evaluated in individuals with MCI to assess the risk of conversion to dementia.

Executive function impairments in individuals with MCI predict conversion to dementia in ACS.

Expert Commentary – Prof. Ming-Chyi Pai

Memory impairment is one of the predictors of MCI-dementia conversion and it is the basis of the current MCI classification, which include amnestic (single domain and multi domains) and non-amnestic MCI.

However, memory is not the only cognitive function to be affected early in AD. It has been suggested that relying only on memory measures may not be optimal for the predictive diagnosis of individuals with MCI – measuring different domains of cognition might be a more balanced approach [Belleville S *et al.,* 2014]. Executive dysfunction is closely related to pathological aging as well as dysfunctions in activities of daily living and has been widely investigated as a predictor of MCI-dementia conversion [Saunders NLJ *et al.,* 2011; Clark LR *et al.,* 2012; Kirova A *et al.,* 2015]. An earlier study has reported that individuals with aMCI with memory and other cognitive domain deficits, including executive function dysfunction, constituted a high-risk group for conversion to AD within 3 years of follow-up [Tabert MH *et al.,* 2006].

The findings by Junquera A, *et al.* corroborated these earlier findings and confirmed that executive function impairment can potentially be used as an early predictor of conversion to AD, even within 1 year of follow-up. As such, evaluating both memory and executive function can improve the accuracy of assessing the risk of progression to dementia in individuals with MCI. Ongoing research continues to employ various models to examine the potentials of imaging markers (e.g. MRI, FDG-PET), biomarkers of AD neuropathology (e.g. β-amyloid), or other neuropsychological measures in predicting MCI-dementia conversion. It is critical to further evaluate the utility of these potential markers in conjunction with each other to develop an optimal algorithm that is clinically relevant in identifying individuals with MCI with a higher risk of progression to dementia.

Reference: Junquera A, *et al.* J Alzheimers Dis 2020;77(2):641–53.

Predictors of rate of cognitive decline in patients with amnestic mild cognitive impairment

Authors: Cerbone B, *et al.*

INTRODUCTION

Substantial research has evaluated factors that can predict conversion from aMCI to AD, but research examining factors predicting rate of decline in aMCI is lacking. As such, this study aimed to systematically examine predictors of rate of decline, including age, ApoE ε4 status, baseline cognitive performance and baseline neuropsychiatric severity, in a longitudinal sample of individuals with MCI.

METHODS

The study included 151 participants (mean age 71.6 years) with single or multidomain aMCI from the ongoing longitudinal study at the Baylor Alzheimer's Disease and Memory Disorder Center. Participants were assessed at baseline and followed up for a mean of 2.32 total visits and a mean of 1.61 years of follow-up. At baseline, all study participants met diagnostic criteria for MCI due to AD [Petersen RC, 2004]. Participants were excluded from the study if their eventual dementia diagnosis was not probable AD.

The cohort of healthy participants from Baylor's Healthy Aging Control Study (control; n=222; age ≥50 years) was utilized for the purpose of developing normative data for analysis.

The study measured:
1. dementia severity – MMSE; the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); and the Clinical Dementia Rating-Sum of Boxes (CDR-SB)
2. episodic memory – Logical Memory and Visual Reproduction I and II subtests of the WMS-R
3. executive functioning – Trail Making Test, Part B (TMT-B); Stroop Color and Word Test, Color-Word Inhibition condition; Letter Fluency; Digit Span Backwards; Similarity subtests of the Wechsler Adult Intelligence Scale (WAIS)
4. semantic fluency – Animal Fluency
5. neuropsychiatric symptoms – NPI-Q; Geriatric Depression Scale (GDS).

Several linear mixed models were then employed to analyze the longitudinal data in this study.
- Model 1 used time and time-squared to predict performance on each cognitive dependent variable.
- Model 2 added covariates (age, education, genetic carrier status and baseline dementia severity) and their interactions with time.
- Model 3 added the cognitive predictors (memory composite, executive functions composite and semantic fluency) and their interactions with time.
- Two additional models included (1) memory severity scores and their interactions with time, and (2) baseline GDS, NPI-Q severity score and their interactions with time.

RESULTS

Predictors of rate of cognitive change

Table 3 summarizes the significant effects of several variables (ApoE ε4 carrier status, cognitive predictors [memory, executive function, semantic fluency] and neuropsychiatric predictors [GDS, NPI-Q]) on dementia severity measures (ADAS-Cog, MMSE and CDR-SB).

Dementia severity measures	Significant predictors of greater dementia severity
ADAS-Cog	Greater baseline of dementia severity*#; lower baseline of memory and executive functions scores#; lower baseline score of semantic fluency#; greater baseline memory severity impairment (four impaired memory scores)†
MMSE	ApoE ε4 carriers*#; greater baseline dementia severity*#; lower baseline of memory and executive functions scores#; greater baseline memory severity impairment (four impaired memory scores)†
CDR-SB	ApoE ε4 carriers*#; greater baseline dementia severity*; lower baseline of memory and executive functions scores#; lower baseline GDS†

Table 3. Significant (*p*-value <0.05) predictors of greater dementia severity as determined by linear mixed model 2 (*), model 3 (#) and additional models (†). Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

Interaction effect with time as a predictor of change on dementia severity measures

Based on linear mixed model 2, there were significant interactions between ApoE ε4 carrier status and time on the ADAS-Cog (p=0.02), MMSE (p=0.01) and CDR-SB (p<0.01) – *ApoE ε4 carriers declined more quickly on all three dementia severity measures compared with non-carriers.* However, interactions of time with age and dementia severity status were not significant (ps>0.05), suggesting that *older individuals did not decline more rapidly in dementia severity.*

Linear mixed model 3 indicated significant interaction effects between executive functions composite score and time as a predictor of change on ADAS-Cog (p=0.01) and CDR-SB (p<0.01) – *individuals with lower baseline executive functions composite scores declined more quickly on dementia severity measures.* There were no significant interactions of time with memory composite score and semantic fluency score for all cognitive dependent variables (ps>0.05).

Interactions of time with memory severity scores (ranging from zero to four impaired tests) indicated that *individuals with four impaired memory scores had faster decline* on the MMSE (p=0.03) and ADAS-Cog (p<0.01) *compared with those with zero impaired memory scores.*

In addition, there were significant interaction effects between GDS and time on the ADAS-Cog (p=0.01) and CDR-SB (p=0.04) – contrary to current literature, individuals with lower scores (GDS≤5) seemed to decline more quickly on dementia severity measures compared with those with higher depression scores. Additional post-hoc analyses found that depression scores within the less-depressed group gradually increased over time, while the reverse was observed within the more-depressed group.

CONCLUSION

Individuals with aMCI who were ApoE ε4 allele carriers, had lower baseline executive function composite score and greater memory impairment severity, and had lower depression level, appeared to decline more rapidly on dementia severity measures. Age, memory composite performance, semantic fluency, cognitive domain impairment status and neuropsychiatric severity did not affect the rate of cognitive decline. These predictors may help identify individuals with aMCI who may decline and convert more quickly to AD, so a more aggressive treatment strategy can be given to delay progression of cognitive decline.

ApoE ε4 status and baseline levels of executive function, memory impairment severity and depression influence rate of cognitive decline in individuals with aMCI.

Expert Commentary – Prof. So Yeon Jeon

Early intervention to slow AD progression is an important strategy as effective symptomatic drugs are limited and disease-modifying drugs are not available. Apart from identifying predictors of high-risk progressors to AD among individuals with MCI, determining factors that may affect the rate of cognitive decline over time is equally important.

The present study highlights that individuals with aMCI who have genetic susceptibility (ApoE ε4 carriers) and more severe memory and executive functioning impairment declined more rapidly in terms of dementia severity. In line with this finding, a previous longitudinal report has suggested that executive functions seem to decline faster compared with memory in individuals with MCI [Johnson JK *et al.,* 2012]. In the present study, overall memory performance was not predictive of faster rate of cognitive decline, but a greater number of impaired memory score was. Indeed, severe memory impairment has been hypothesized to be associated with more extensive neurodegeneration and AD pathophysiological process; therefore, it contributes to faster cognitive decline.

A noteworthy finding reported by Cerbone B, et al. concerned the rate of cognitive decline in study subjects with a higher level of depression. In contrast to reports in current literature, those with higher depression level demonstrated slower rate of cognitive decline compared with those with lower depression level. It was speculated that participants with high depression level were more likely to be treated, contributing to the positive cognitive effects and thus the slower rate of cognitive decline. It would be interesting to further confirm this finding – treatment of depression with selective serotonin-reuptake inhibitor has been found to delay progression to clinically diagnosed AD [Bartels C *et al.,* 2018], highlighting the importance of treating depression to reduce AD risk. Future studies would also benefit from the inclusion of biomarkers of AD pathology (e.g. β-amyloid or tau) and whether similar findings can be observed in real-world settings.

Reference: Cerbone B, *et al.* Clin Neuropsychol 2020;1–27.

MRI and cognitive scores complement each other to accurately predict Alzheimer's dementia 2 to 7 years before clinical onset

Authors: Zandifar A, *et al.*

INTRODUCTION

Approximately 10–15% of individuals with aMCI progress to clinically probable AD. As such, predicting if and when an individual with aMCI will have future dementia is of high value for the prevention of cognitive decline. Studies have shown that volumetric MRI is able to capture anatomical atrophy that is present ahead of cognitive decline, rendering its measure a promising biomarker for early prediction. Additionally, cognitive state can also predict future cognitive decline in individuals with aMCI. This study aimed to evaluate the utility of baseline cognitive scores and MRI biomarkers in predicting the onset of dementia due to AD in a population with aMCI over a 9-year follow-up period.

METHODS

All subjects with MCI from the datasets of Alzheimer's Disease Neuroimaging Initiative (ADNI)1, ADNI2 and ADNI-GO with available baseline neurocognitive scores and T1 MRI (n=756) were included in this study. Study measures included MRI-derived biomarker and baseline neurocognitive scores that were available within the ADNI study **(Table 4).**

MRI-derived biomarkers	Neurocognitive scores	Demographics
Hippocampal and entorhinal SNIPE grading scores	Total score of ADAS-Cog (ADAS-Cog-11 and ADAS Cog-13)	Age
	Rey Auditory Verbal Learning Task scores of immediate recall, learning and forgetting	Gender
	MMSE	Years of education
	CDR-SB	

Table 4. MRI and neurocognitive features, as well as demographics used in the study. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; SNIPE, Scores by Nonlocal Image Patch Estimator.

Three classifier scenarios were trained based on the following baseline features:

1. Using only four MRI-driven biomarkers (both left and right entorhinal and hippocampal Scores by Nonlocal Image Patch Estimator [SNIPE] score) and age, gender and years of education;

2. Using only seven neurocognitive scores and age, gender and years of education;

3. Using all MRI-driven and neurocognitive scores together, and age, gender and years of education.

Over a 9-year follow-up period, a Naïve Bayes classifier was built each year and tested with Leave One Out cross-validation. The classification performance at each time point was assessed through its accuracy, sensitivity, specificity, and area under the receiver operating curve (AUC); the latter provides a more robust measurement against data imbalance. Feature importance over time in relation to disease progression was also determined over the 9-year follow-up period.

RESULTS

Classification performance

From 2 years onwards, the classification accuracy using both MRI and neurocognitive features were better than using only MRI or neurocognitive features. MRI features were more sensitive, while neurocognitive features provide specificity to the prediction. The AUC plot over time showed 87% accuracy, 86% sensitivity and 89% specificity of prediction of the combined features at 5 years of follow-up, with an AUC>0.85 for follow-up periods from 2 to 7 years.

Feature importance in predicting progression

ADAS-Cog demonstrated the greatest importance over the entire follow-up period, followed by hippocampal SNIPE scores.

Although all features lost AD-related sensitivity over long follow-up period, the peak importance of each feature occurred at a different follow-up time point. Importantly, the farther a peak occurs relative to the baseline, the more sensitive the corresponding feature is to the early changes of AD-related pathology.

When used alone, entorhinal cortex was among the first biomarkers to show abnormality (peak at 68 months). While hippocampal grading score peaked at 39 months, it showed a higher importance for all follow-up periods from 1 to 7 years compared with the entorhinal cortex SNIPE score. The Rey Auditory Verbal Learning Task scores (peak at 62 months) were more sensitive to early AD changes when compared with MMSE (peak at 47 months) and CDR-SB (peak at 19 months). Age, gender and years of education exhibited very low importance with respect to other features.

CONCLUSIONS

MRI biomarkers are highly sensitive to abnormal morphological changes in the brain (i.e. identify at-risk subjects), whereas preservation of cognitive function helps to identify individuals who will not progress over time despite changes in MRI biomarkers. The combination of both features as a prognostic tool can yield a more accurate, sensitive and specific result. Such a tool will be useful in early identification of individuals that would benefit from interventions that could delay cognitive decline and onset of dementia.

MRI biomarkers and cognitive scores complement each other in providing a highly sensitive and specific prediction years before the onset of dementia.

Expert Commentary – Dr. Chi-Leung Lam

We know that not all individuals with MCI will progress to dementia. In clinical practice, we try to identify those patients who are at risk of disease progression, as the literature has informed us that multidomain lifestyle intervention, combining healthy diet, exercise and cognitive training, is a successful preventive strategy [Kivipelto M *et al.,* 2020].

Despite the high variability related to an individual, imaging technology and methodology, the utility of a sophisticated brain MRI is shifting from an exclusion criterion in evaluating and diagnosing neurocognitive disorders to one of the most promising inclusion criteria (as biomarkers) because of its wide availability and non-invasive nature [Duchesne S *et al.,* 2010].

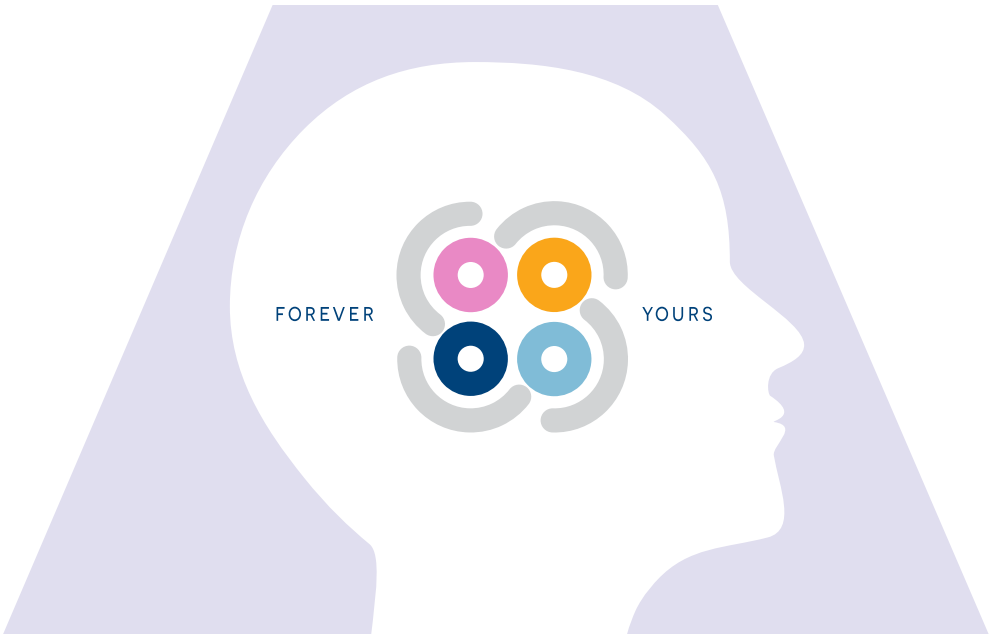
This Canadian study by Zandifar A, *et al.* (2019) adds to the accumulating evidence that volumetric MRI measure at both hippocampal and entorhinal areas when combined with standardized neurocognitive tests can predict future development of AD in individuals with aMCI. In addition, the study is unique in using SNIPE to compare the structural similarity of the hippocampal and entorhinal areas to a library of cognitively normal individuals or individuals with AD. On the other hand, we need to recognize that the study findings may not be applicable to individuals with other subtypes of MCI and dementia.

The application of structural or functional imaging for neurocognitive disorders in Hong Kong is slowly growing in the recent decade. Both manual and automated analysis of the brain MRI are now available [Zhao L *et al.,* 2019]. In my opinion, the future biomarkers for predicting MCI and dementia will likely be a combination of a few minimally invasive, accessible and affordable parameters that can provide high specificity and sensitivity in identifying disease progression. This will enable us, the clinicians, to identify at-risk individuals and provide them with individualized interventions well in advance.

Reference: Zandifar A, *et al.* Neuroimage Clin 2020;25:102121.

References

Bartels C, *et al.* Am J Psychiatry 2018;175:232–41; Belleville S, *et al.* Neuropsychology 2014;28(4):643–52; Cerbone B, *et al.* Clin Neuropsychol 2020;1–27; Clark LR, *et al.* J Int Neuropsychol Soc 2012;18:118–27; Duchesne S, *et al.* Neurobiology of Aging 2010;31:1606–1617; Johnson JK, *et al.* Brain Imaging Behav 2012;6(4):540–50; Junquera A, *et al.* J Alzheimers Dis 2020;77(2):641–53; Kirova A, *et al.* Biomed Res Int 2015;2015:748212; Kivipelto M, *et al.* Alzheimers Dement 2020;16(7):1078–94; Petersen RC. J Intern Med 2004;256(3):183–94; Saunders NLJ, *et al.* Neuropsychology 2011;25:237–48; Tabert MH, *et al.* Arch Gen Psychiatry 2006;63(8):916–24; Zandifar A, *et al.* Neuroimage Clin 2020;25:102121; Zhao L, *et al.* Aging (Albany NY) 2019;11(16):6217–6236.



donepezil hydrochloride

Aricept®

HI-Eisai

hhc human health care

PH-AR-AD-21C-08

Donepezil Aricept Abridge Product Information

1. FORMULATION

Each orodispersible tablet contains 5 or 10 mg of Donepezil Hydrochloride.

2. CLINICAL PARTICULARS

2.1 Therapeutic indications
Donepezil hydrochloride (Aricept Evess®) tablets are indicated for the symptomatic treatment of:
- mild, moderate and severe Alzheimer's disease
- vascular dementia (dementia associated with cerebrovascular disease)
- dementia with Lewy bodies (DLB)

2.2 Dosage and method of administration

Adults/Elderly:
Treatment is initiated at 5mg/day (once-a-day dosing). Donepezil hydrochloride (ARICEPT EVESS®) should be taken orally, in the evening just prior to retiring or as prescribed by physician. The tablet should be placed on the tongue and allow to disintegrate before swallowing with or without water, according to patient preference. The 5mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved. Following a 4-6 weeks clinical assessment in patient who tolerated treatment at 5mg/day, the dose of Donepezil hydrochloride (ARICEPT EVESS®) can be increased to 10mg/day (once-a-day dosing).

For patient with DLB, the dose may be decreased to 5mg depending on the symptoms of the patient.
Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to accepted guidelines. Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exist. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted.
Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil hydrochloride is seen. There is no evidence of a rebound or withdrawal effect after abrupt discontinuation of the therapy.

Renal and Hepatic Impairment:
A similar dose schedule can be followed for patients with renal or mild to moderate hepatic impairment because clearance of donepezil hydrochloride is not significantly affected by these conditions.

Children
Donepezil hydrochloride and well controlled trials to document the safety and efficacy of donepezil hydrochloride in any illness occurring in children.

2.3 Contraindications

Donepezil hydrochloride is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

2.4 Special warnings and precautions for use

Anesthesia: Donepezil hydrochloride, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during the anaesthesia.
Cardiovascular Conditions: Cholinesterase inhibitors may have vagatonic effects on heart rate (e.g., bradycardia).
Gastrointestinal Conditions: Cholinomimetics may promote gastric acid production. Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs).
Donepezil hydrochloride, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10mg/day dosage than with the 5mg/day dosage. Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil hydrochloride, patients should be observed closely at the initiation of treatment and after does increases.

Neurological Conditions: Cholinomimetics are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. The administration of Donepezil hydrochloride concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Sever Hepatic Impairment: There are no data for patients with severe hepatic impairment.

Mortality in Vascular Dementia Clinical Trials
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however this difference was not statistically significant. The majority of deaths taking either donepezil hydrochloride or placebo appear to result from various vascular related causes which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo. In pooled Alzheimer's disease studies (n=4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

2.5 Interaction with other medicinal products and other forms of interaction
The administration of donepezil hydrochloride concomitantly with other cholinesterase inhibitors should be avoided. Donepezil hydrochloride and its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridazine, risperidone, and sertraline in human. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin, cimetidine, thioridazine, risperidone and sertraline. In a study of Parkinson's disease patients on optimal treatment with L-dopa/carbidopa, administration of donepezil hydrochloride for 21 days had no effects on L-dopa or carbidopa blood levels. In this study, no effects on motor activity were observed. Drug interaction studies performed in vitro show that ketoconazole and quinidine, known as inhibitors of CYP3A4 and CYP2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. These increases are smaller than those produced by ketoconazole for other agents sharing the CYP3A4 pathway. Administration of donepezil had no effect on the pharmacokinetics of ketoconazole.

The influence of CYP2D6 on donepezil clearance was further explored via population pharmacokinetic (PK) analysis in a controlled clinical study of donepezil 10 mg in patients with moderately severe to severe AD. In the PK database for Study 326, there were 31 patients classified as poor metabolizers, 508 patients classified as extensive metabolizers, 13 patients classified as ultra-rapid metabolizers, and 298 patients whose CYP2D6 phenotype was not classified. The largest subtype was the extensive metabolizer group and was used as the reference group. Small differences in clearance values were observed among the CYP2D6 subgroups. When compared to the extensive metabolizers, the poor metabolizers group had a 31.5% lower clearance and the ultra-rapid metabolizer group had a 24% higher clearance. While the differences among groups were relatively small, the results indicate that donepezil is eliminated, in part, via CYP2D6 metabolism. Overall, these results suggest CYP2D6 does not significantly contribute to the metabolism of donepezil.

Based on in vitro studies, donepezil shows little or no evidence of direct inhibition of CYP2B6, CYP2C8 and CYP2C19 at clinically relevant concentrations.

Enzyme inducers, such as rifampicin, phenytoin, carbamazepine, and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combination should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving such medications as succinylcholine and other neuromuscular blocking agents. There is also a potential for synergistic activity with cholinergic agonists or bet blocking agents which have effects on cardiac conduction.
Donepezil was not a substrate of P-glycoprotein in an in vitro study.

2.6 Undesirable effects

Mild to Moderately Severe Alzheimer's Disease
The most common adverse events (incidence ≥ 5% and twice the frequency of placebo in patients receiving 10mg/day) were diarrhea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Other common adverse events (incidence ≥ 5% and ≥ placebo) were headache, pain, accident, common cold, abdominal disturbance and dizziness. Cases of syncope, bradycardia, sinoatrial block and atrioventricular block were observed. No notable abnormalities in laboratory values associated with the treatment were observed except for minor increases in serum concentrations of muscle creatinine kinase.

Severe Alzheimer's Disease
The most common adverse events (incidence ≥ 5% and twice the frequency of placebo) were diarrhea, nausea, and aggression.

Vascular Dementia

A comparison of the Alzheimer's disease and vascular dementia studies shows that the types of and relative proportions of adverse events associated with donepezil hydrochloride were similar in the two populations.

Dementia with Lewy Bodies
The safe profile observed in the Phase 3 study in patients with Dementia with Lewy Bodies was similar to the safety profile observed in the studies in Alzheimer's Disease with the exception of a higher rate of Parkinsonism.

Post-Marketing Experience
There have been post-marketing reports of hallucinations, agitation, aggressive behaviour, seizure, hepatitis, gastric ulcer, duodenal ulcer, and gastrointestinal hemorrhage.

3. PHARMACOLOGICAL PROPERTIES

3.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for dementia, ATC code: N06DA02
Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

3.2 Pharmacokinetic properties

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximately steady-state is achieved within 3 weeks after the initiation of the therapy. Once at steady-state, plasma donepezil hydrochloride concentrations and the related pharmacodynamics activity show little variability over the course of the day.

Food does not affect the absorption of donepezil hydrochloride.

Distribution: Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5mg dose of ^{14}C-labeled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil is hepatically metabolized and the predominant route for the elimination of both parent drug and its metabolites is renal, as 79% of the recovered dose was found in the urine with the remaining 21% found in the feces. Moreover, the parent compound, donepezil, is the predominant elimination product in urine. The major metabolites of donepezil include M1 and M2 (via *O*-dealkylation and hydroxylation), M11 and M12 (via glucuronidation of M1 and M2 respectively), M4 (via hydrolysis) and M6 (via *N*-oxidation). Plasma donepezil concentrations decline with a half-life of approximately 70 hours.

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly

subjects, or in Alzheimer's or vascular dementia patients. However mean plasma levels in patients closely agreed with those of young healthy volunteers.

There was a relationship noted between body weight and clearance. Over the range of body weight from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/hr for 70 kg individuals.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Full prescribing information available.

Reporting of Suspected Adverse Reactions
Please Contact: HI-Eisai Pharmaceutical, Inc. +632 88875837 / +632 88875160 / +63 9088672236
Or Report to FDA Philippines: www.fda.gov.ph

MARKETING AUTHORIZATION NUMBER
5 mg Orodispersible Tablets: DR-XY35549
10 mg Orodispersible Tablets: DR-XY35548

Manufactured by:
Bushu Pharmaceuticals Ltd. Misato Factory
950, Hiroki, Ohaza, Misato-machi, Kodama-gun,
Saitama-ken, Japan
Under License of Eisai Co., Ltd.

Imported by:
HI-Eisai Pharmaceutical, Inc.
Unit 2, 22F, Tower 6789
6789 Ayala Avenue, Makati City, 1226 Philippines

Under License from:
EISAI Co., Ltd.
4-6-10 Koishikawa,
Bunkyo-ku, Tokyo, Japan

Suggested Retail Price:
P 126/5mg tab, P 164/10mg tab, P 160/23mg tab

Date of Production of Material: March 2021
PH-AR-AD-21C-08

Donepezil hydrochloride
Aricept®
23 mg Film-Coated Tablet
Cholinesterase Inhibitor

1. INDICATIONS
Donepezil hydrochloride (ARICEPT®) 23 mg tablet is a cholinesterase inhibitor indicated for the symptomatic treatment of moderate to severe Alzheimer's disease.

2. DOSAGE AND ADMINISTRATION
Donepezil hydrochloride (ARICEPT®) 23 mg tablets can be taken once daily in the evening just prior to retiring and can be taken with or without food or as prescribed by the physician. Donepezil hydrochloride (ARICEPT®) 23 mg tablets should not be split or crushed and should be swallowed whole with water.

The recommended starting dose of donepezil hydrochloride is 5 mg once daily. A dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Patients who have been established on 10 mg of donepezil hydrochloride daily for at least 3 months can be administered one Donepezil hydrochloride (ARICEPT®) 23 mg tablets once daily.

3. COMPOSITION, DOSAGE FORM & STRENGTH
Donepezil hydrochloride (ARICEPT®) 23 mg tablets is supplied as reddish, round, filmcoated, containing 23 mg of donepezil hydrochloride. The strength in mg (23) is debossed on one side, and "ARICEPT" is debossed on the other side.

4. CONTRAINDICATIONS
Donepezil hydrochloride (ARICEPT®) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride, piperidine derivatives or to any excipients used in the formulation.

5. WARNINGS AND PRECAUTIONS
5.1. Anesthesia
Donepezil hydrochloride (ARICEPT®) 23 mg tablets, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

5.2. Cardiovascular Conditions
Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of Donepezil hydrochloride (ARICEPT®) 23 mg tablets.

5.3. Nausea and Vomiting
Donepezil hydrochloride (ARICEPT®), as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose, and more frequently with the 23 mg dose than with the 10 mg dose. Specifically, in a controlled trial that compared a dose of 23 mg/day to 10 mg/day in patients who had been treated with donepezil 10 mg/day for at least three months, the incidence of nausea in the 23 mg group was markedly greater than in the patients who continued on 10 mg/day (11.8% vs 3.4%, respectively), and the incidence of vomiting in the 23 mg group was markedly greater than in the 10 mg group (9.2% vs 2.5%, respectively). The percent of patients who discontinued treatment due to vomiting in the 23 mg group was markedly higher than in the 10 mg group (2.9% vs 0.4%, respectively). Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT, patients should be observed closely at the initiation of treatment and after dose increases.

5.4. Peptic Ulcer Disease and GI Bleeding
Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Results of a controlled clinical study of Donepezil hydrochloride (ARICEPT®) 23 mg tablets showed an increase relative to donepezil hydrochloride 10 mg/day, in the incidence of peptic ulcer disease (0.4% vs. 0.2%) and gastrointestinal bleeding from any site (1.1% vs. 0.6%).

5.5. Weight Loss
Weight loss was reported as an adverse event in 4.7% of patients assigned to Donepezil hydrochloride (ARICEPT®) 23 mg tablets compared to 2.5% of patients assigned to 10 mg donepezil hydrochloride.

5.6. Genitourinary Conditions
Although not observed in clinical trials of Donepezil hydrochloride (ARICEPT®), cholinomimetics may cause bladder outflow obstruction.

5.7. Neurological Conditions: Seizures
Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

5.8. Pulmonary Conditions
Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

5.9. Mortality in Vascular Dementia Clinical Trials
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDSAIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%). However, this difference was not statistically significant.

The majority of deaths in patents taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo. In pooled Alzheimer's disease studies (n=4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

6. ADVERSE REACTIONS
6.1 Undesirable effects
The most common adverse events are diarrhea, muscle cramps, fatigue, nausea, vomiting and insomnia.
The incidence profile for adverse events for severe Alzheimer's disease is similar to that of mild to moderately severe Alzheimer's disease. The table below reflects the incidence of adverse events in patients receiving treatment with Donepezil hydrochloride (ARICEPT®) for all stages of Alzheimer's disease.

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,100), very rare (< 1/10,000) and not known (cannot be estimated from available data).

System Organ Class	Very common	Common	Uncommon	Rare
Infections and infestations		Common cold		
Metabolism and nutrition disorder		Anorexia		
Psychiatric disorders		Hallucinations**, Agitation**, Aggressive behaviour**		
Nervous system disorder		Syncope*, Dizziness, Insomnia	Seizure*	Extrapyramidal symptoms
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block
Gastrointestinal disorders	Diarrhea, Nausea	Vomiting, Abdominal disturbance	Gastrointestinal haemorrhage, Gastric and Duodenal ulcers	
Hepato-biliary disorders				Liver dysfynction including hepatitis***
Skin and subcutaneous tissue		Rash, Pruritus		
Musculoskeletal, connective tissue and bone disorders		Muscle cramps		
Renal and urinary disorders		Urinary incontinence		
General disorders and administration site conditions	Headache	Fatigue, Pain		
Investigations			Minor increase in serum concentration of muscle creatine kinase	
Injury and poisoning		Accident		

* In investigating patients for syncope or seizure, the possibility of heart block or long sinusal pauses should be considered
** Reports of hallucinations, agitation, aggressive behavior have resolved on dose-reduction or discontinuation of treatment.
*** In cases of unexplained liver dysfunction, withdrawal of Donepezil hydrochloride (ARICEPT®) should be considered.

7. DRUG INTERACTIONS

7.1. Effect of Donepezil hydrochloride (ARICEPT®) 23 mg tablets on the Metabolism of Other Drugs

No in vivo clinical trials have investigated the effect of donepezil hydrochloride on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, in vitro studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether Donepezil hydrochloride (ARICEPT®) 23 mg tablets has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of donepezil for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of donepezil on the pharmacokinetics of these drugs were observed.

7.2. Effect of Other Drugs on the Metabolism of Donepezil hydrochloride (ARICEPT®) 23 mg tablets

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease. Donepezil clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with a known CYP2D6 inhibitor. This result is consistent with the conclusion that CYP2D6 is a minor metabolic pathway of donepezil.

Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexa methasone, rifampin, and phenobarbital) could increase the rate of elimination of Donepezil hydrochloride (ARICEPT®) 23 mg tablets.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil is not significantly affected by concurrent administration of digoxin or cimetidine.

7.3. Use with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

7.4. Use with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

8. CLINICAL PHARMACOLOGY

8.1. Pharmacodynamics (Mechanism of Action)

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.

8.2. Pharmacokinetics

Based on population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease, following oral dosing, peak plasma concentration is achieved for Donepezil hydrochloride (ARICEPT®) 23 mg tablets in approximately 8 hours, compared with 3 hours for Donepezil hydrochloride (ARICEPT®) 10 mg tablets. Peak plasma concentrations were almost 2-fold higher for ARICEPT 23 mg tablets than Donepezil hydrochloride (ARICEPT®) 10 mg tablets.

The elimination half-life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13-0.19 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 12-16 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.

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of 14C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. Examination of the effect of CYP2D6 genotype in Alzheimer's patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance. These results suggest CYP2D6 has a minor role in the metabolism of donepezil.

Hepatic Disease: In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Renal Disease: In a study of 11 patients with moderate to severe renal impairment (Cl_C < 18 mL/min/1.73 m^2) the clearance of donepezil did not differ from 11 age- and sex-matched healthy subjects.

Age: No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of Donepezil hydrochloride (ARICEPT®) 23 mg tablets. Population pharmacokinetic analysis suggested that the clearance of donepezil in patients decreases with increasing age. When compared with 65-year old subjects, 90-year old subjects have a 17% decrease in clearance, while 40-year old subjects have a 33% increase in clearance. The effect of age on donepezil clearance may not be clinically significant.

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of Donepezil hydrochloride (ARICEPT®). However, retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease indicate that gender and race (Japanese and Caucasians) did not affect the clearance of Donepezil hydrochloride (ARICEPT®) to an important degree.

Body weight: There was a relationship noted between body weight and clearance. Over the range of weights from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/hr for 70 kg individuals.

Drugs Highly Bound to Plasma Proteins: Drug displacement studies have been performed in vitro between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3-10 μg/mL did not affect the binding of furosemide (5 μg/mL), digoxin (2 ng/mL), and warfarin (3 μg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Full prescribing information available.

Reporting of Suspected Adverse Reactions

Please Contact: HI-Eisai Pharmaceutical, Inc. +632 88875837 / +632 88875160 / +63 9088672236
Or Report to FDA Philippines: www.fda.gov.ph

Suggested Retail Price:

P 126/5mg tab, P 164/10mg tab, P 160/23mg tab

MARKETING AUTHORIZATION NUMBER

DR No. XY42383

Manufactured by:
Eisai Co., Ltd. (Kawashima Plant)
1, Kawashimatakehaya-machi
Kakamigahara-shi, Gifu-ken, Japan

Imported by:
HI-Eisai Pharmaceutical, Inc.
Unit 2, 22F, Tower 6789
6789 Ayala Avenue, Makati City, 1226 Philippines

Date of Production of Material: March 2021
PH-AR-AD-21C-08