

Revised: May 2011 (5th version)

Standard Commodity Classification No. of Japan
87119

- For the treatment of dementia of the Alzheimer's type -

Aricept[®] Oral Jelly 3 mg
Aricept[®] Oral Jelly 5 mg
Aricept[®] Oral Jelly 10 mg

<Donepezil Hydrochloride preparation>

Powerful drug and Prescription drug

Storage	Oral Jelly 3 mg	Oral Jelly 5 mg	Oral Jelly 10mg
ARICEPT Oral Jelly should be stored at room temperature.	APPROVAL NO.	22100AMX02091000	22100AMX02095000 22100AMX02096000
Expiration date	Date of listing in the NHI reimbursement price	Nov 2009	
ARICEPT Oral Jelly should be used before the expiration date on the package or label.	Date of initial marketing in Japan	Dec 2009	
	International birth date	Nov 1996	

Caution: See "PRECAUTIONS FOR HANDLING" section.

Caution: Use only as directed by a physician.

CONTRAINDICATIONS (ARICEPT Oral Jelly is contraindicated in the following patients.)**Patients with a history of hypersensitivity to any ingredients of ARICEPT Oral Jelly or piperidine derivatives****DESCRIPTION**

Brand name	Active ingredient/content in each cup (10 g)	Inactive ingredients	Dosage form	pH
ARICEPT Oral Jelly 3 mg	Donepezil hydrochloride 3 mg	Acesulfame potassium, sodium benzoate, calcium disodium edetate hydrate, carrageenan, citric acid hydrate, sodium citrate hydrate, calcium lactate hydrate, ethyl parahydroxybenzoate, propylene glycol, powdered hydrogenated maltose starch syrup, pectin, flavor, benzyl benzoate, ethanol, vanillin	Jelly for internal use	3.2~4.0
ARICEPT Oral Jelly 5 mg	Donepezil hydrochloride 5 mg			
ARICEPT Oral Jelly 10 mg	Donepezil hydrochloride 10 mg			
Brand name	Appearance (Shape of a cup)		Description	
ARICEPT Oral Jelly 3 mg			White to light-yellowish jelly with a characteristic smell or without smell.	
ARICEPT Oral Jelly 5 mg				
ARICEPT Oral Jelly 10 mg				

INDICATIONS

Suppression of progression of demential symptoms in dementia of the Alzheimer's type

<Precautions>

1. ARICEPT Oral Jelly should be administered only to

patients diagnosed as having dementia of the Alzheimer's type.

2. It has not been demonstrated that ARICEPT Oral Jelly suppresses the progression of the pathological state of dementia of the Alzheimer's type itself.
3. The efficacy of ARICEPT Oral Jelly has only been established for dementia of the Alzheimer's type, not for other types of dementia.

DOSAGE AND ADMINISTRATION

The usual initial adult dose for oral use is 3mg of donepezil hydrochloride once daily. After 1 to 2 weeks the dosage is increased to 5mg. The dosage for patients with severe dementia of Alzheimer's type is increased to 10mg after dosing at 5mg for 4 or more weeks. The dose should be reduced appropriately according to patients' symptoms.

<Precaution>

1. The dosage of 3mg/day is not an effective dose but is given to inhibit gastrointestinal adverse reactions. At this dose ARICEPT Oral Jelly should not be administered for more than 1 to 2 weeks in principle.
2. When increasing the administered dose to 10mg daily, care should be observed with regard to gastrointestinal related adverse reactions.
3. ARICEPT Oral Jelly should be administered under the supervision of medical professionals or family, etc.

PRECAUTIONS**1. Careful Administration (ARICEPT Oral Jelly should be administered with care in the following patients.)**

ARICEPT Oral Jelly is an acetylcholinesterase inhibitor and should be administered with care to the following pa-

tients in whom it may induce or aggravate symptoms of their disease due to its cholinergic action.

- (1) Patients with such heart diseases as sick sinus syndrome, intra-atrial and atrioventricular junctional conduction disturbances.

[ARICEPT Oral Jelly may cause bradycardia or arrhythmia due to its vagotonic action.]

- (2) Patients with a history of peptic ulcer or who are receiving nonsteroidal anti-inflammatory analgesics

[ARICEPT Oral Jelly may aggravate peptic ulcer by increasing gastric acid secretion or digestive tract motility.]

- (3) Patients with a history of bronchial asthma or obstructive pulmonary disease

[ARICEPT Oral Jelly may aggravate their symptoms by promoting the contraction of bronchial smooth muscle, or bronchial secretory action.]

- (4) Patients with extrapyramidal disorders (Parkinson's disease or Parkinson's syndrome, etc.)

[ARICEPT Oral Jelly may induce or aggravate symptoms by promoting cholinergic nerve activity in the corpus striatum.]

2. Important Precautions

- (1) Bradycardia, heart block (Sinoatrial block or atrioventricular block) and QT prolongation, etc. may occur after administering ARICEPT Oral Jelly. In particular, patients with cardiac disorders (myocardial infarction, valvular disorder and cardiomyopathy and others) and/or with electrolyte abnormalities (hypokalemia, etc.), should be carefully observed to prevent serious arrhythmia developing.

- (2) In diagnosis, caution should be taken to carefully distinguish between Alzheimer's disease and other types of dementia.

- (3) Avoid prolonged administration if efficacy of ARICEPT Oral Jelly is not observed.

- (4) The administration of ARICEPT Oral Jelly concomitantly with other acetylcholinesterase inhibitors (galantamine, etc.) should be avoided.

3. Drug Interactions

ARICEPT Oral Jelly is metabolized mainly by CYP3A4 and partially by CYP2D6. [See "PHARMACOKINETICS" section.]

Precautions for coadministration (ARICEPT Oral Jelly should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Suxamethonium chloride hydrate	Possible potentiation of muscle relaxation.	ARICEPT Oral Jelly may potentiate the depolarizing muscle relaxation activity of the coadministered drug.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Cholinomimetics Acetylcholine chloride Carpronium chloride Bethanechol chloride Aclatonium napadisilate Cholinesterase inhibitors Ambenonium chloride Distigmine bromide Pyridostigmine bromide Neostigmine, etc.	Possible potentiation of cholinergic activity, such as vagal activity.	Both drugs have cholinergic activity.
Itraconazole Erythromycin, etc.	May inhibit metabolism of ARICEPT Oral Jelly and potentiate its action.	Due to inhibition of cytochrome P450 (CYP3A4) by coadministered drug.
Quinidine sulfate hydrate, etc.		Due to inhibition of cytochrome P450 (CYP2D6) by coadministered drug.
Carbamazepine Dexamethazone Phenytoin Phenobarbital Refampicin, etc.	May promote metabolism of ARICEPT Oral Jelly and diminish its action.	Due to induction of cytochrome P450 (CYP3A4) by coadministered drug.
Central anticholinergics Trihexyphenidyl hydrochloride Piroheptine hydrochloride Mazaticol hydrochloride hydrate Metixene hydrochloride Biperidene hydrochloride Atropine anticholinergics Scopolamine butylbromide Atropine sulfate hydrate, etc.	ARICEPT Oral Jelly and anticholinergics may interfere with each other and diminish each other's effects.	The actions of ARICEPT Oral Jelly and anticholinergics antagonize each other.
Nonsteroidal anti-inflammatory analgesics	May cause peptic ulcer.	Gastric acid secretion is promoted due to activation of cholinergic system.

4. Adverse Reactions

Mild to moderate dementia of the Alzheimer's type

In clinical trials conducted before approval, adverse reactions were reported in 48 of 457 patients (10.5%). Also, laboratory abnormalities were reported in 98 patients (21.4%). (At the time of approval)

In the treatment outcome study, adverse reactions (including laboratory abnormalities) were reported in 346 of 3240 patients (10.7%). (At the end of reexamination period)

Severe dementia of the Alzheimer's type

In clinical trials conducted before approval, adverse reactions (including laboratory abnormalities) were reported in 171 of 386 patients (44.3%). (At the time of approval)

(1) Clinically significant adverse reactions

1) Syncope, bradycardia, heart block, QT prolongation, myocardial infarction and heart failure

Syncope (< 0.1%), bradycardia (1% > ≥0.1%), heart block (sinoatrial block or atrioventricular block), QT prolongation (< 0.1%), myocardial infarction (<0.1%) or heart failure (< 0.1%) may occur. In the event of such symptoms, appropriate measures, such as discontinuation of the medication, should be taken.

2) Peptic ulcer, perforating duodenal ulcer and gastrointestinal hemorrhage

ARICEPT Oral Jelly may cause peptic ulcer (gastric/duodenal ulcer) (< 0.1%), perforating duodenal ulcer (incidence unknown) or gastrointestinal hemorrhage (< 0.1%) by increasing gastric acid secretion or digestive tract motility due to its activation of the cholinergic system. In the event of such symptoms, appropriate measures such as discontinuation of the medication should be taken.

- 3) **Hepatitis, hepatic function disorders and jaundice**
Hepatitis (incidence unknown), hepatic function disorders (1%>≥0.1%) or jaundice (incidence unknown) may occur. In the event of abnormal findings, appropriate measures such as discontinuation of the medication should be taken.
- 4) **Cerebral seizures, cerebral haemorrhage and cerebrovascular disorder**
Cerebral seizures (epilepsy or convulsions, etc.) (1%>≥0.1%), cerebral haemorrhage (< 0.1%) or cerebrovascular disorder (< 0.1%) may occur. In the event of such symptoms, appropriate measures such as discontinuation of the medication should be taken.
- 5) **Extrapyramidal disorders (1%>≥0.1%)**
Extrapyramidal disorders such as hypokinesia, ataxia, dyskinesia, dystonia, tremor, involuntary movements, abnormal gait, abnormal posture or speech disorder may occur. In the event of such symptoms, appropriate measures such as discontinuation of the medication should be taken.
- 6) **Malignant syndrome (Syndrome malin) (< 0.1%)**
Akinetic mutism, extreme muscle rigidity, dysphagia, tachycardia, blood pressure fluctuation or diaphoresis etc. may occur. In the event that such symptoms are accompanied by hyperpyrexia, the medication should be discontinued and systemic treatment such as cooling, fluid and electrolyte infusion with intensive treatment should be taken. Increase in WBC and serum CK (CPK) tend to occur and renal function disorders with myoglobinuria may also be observed.
- 7) **Rhabdomyolysis** (incidence unknown) Since rhabdomyolysis may occur, patients should be carefully observed for myalgia, weakness, elevations of CK (CPK), or blood and urine myoglobin, etc. In the event of such symptoms, treatment should be discontinued and appropriate measures taken. Caution should be exercised with respect to acute renal failure due to rhabdomyolysis.
- 8) **Dyspnea (< 0.1%)** Dyspnea may occur. In the event of such symptom, the medication should be discontinued and appropriate measures taken.
- 9) **Acute pancreatitis** (incidence unknown) Acute pancreatitis may occur. In the event of abnormal findings, appropriate measures such as discontinuation of the medication should be taken.
- 10) **Acute renal failure (< 0.1%)** Acute renal failure may occur. In the event of abnormal findings, ap-

propriate measures such as discontinuation of the medication should be taken.

11) Sudden death of unknown origin (< 0.1%)

(2) Other adverse reactions

	3%>≥1%	1%>≥0.1%	<0.1%	Incidence unknown
Hypersensitivity ^{note)}		Rash and itching		
Gastrointestinal	Anorexia, nausea, vomiting and diarrhea	Abdominal pain, constipation and salivation	Dysphagia and fecal incontinence	
Psychoneurologic		Excitement, unrest, insomnia, sleepiness, hallucination, aggressiveness, delirium, delusion and hyperkinesia	libido increased, talkativeness, manic state, mental depression, confusion and indifference	Nightmare
Central and peripheral nervous system		Parosmia, tremor, headache, and dizziness	Stupor	
Hepatic		Elevation of LDH, AST (GOT), ALT (GPT), γ-GTP and ALP		
Cardiovascular		Palpitations and increase in blood pressure	Decrease in blood pressure	Atrial fibrillation
Urinary		Elevation of BUN	Urinary incontinence and urinary frequency	Urinary retention
Hematologic		Leukopenia, decrease in hematocrit and anemia	Thrombocytopenia	
Others		Elevation of CK (CPK), total cholesterol, triglycerides, amylase, urine amylase. Malaise, edema and falls	Facial hot flushes, weakness, chest pain and myalgia,	Diaphoresis, facial edema and fever

Note). In the event of such symptoms, treatment should be discontinued.

The incidences in the above table are based on the results of clinical trials (mild to moderate / severe dementia of the Alzheimer's type) and the treatment outcome study (mild to moderate dementia of the Alzheimer's type).

5. Use during Pregnancy, Delivery or Lactation

- (1) ARICEPT Oral Jelly should be used in pregnant women or women suspected of being pregnant only if the expected therapeutic benefit outweighs the possible risk of treatment.
[Decreases in delivery rate of live neonates, increase in incidence of stillbirth and suppression of body weight gain after birth have been observed with donepezil hydrochloride in an animal study (10mg/kg p.o. in rats).]
- (2) It is advisable to avoid administration to nursing mothers. When ARICEPT Oral Jelly must be used, breast feeding should be discontinued during treatment.
[When ¹⁴C-donepezil hydrochloride was administered orally to rats, it was found to be excreted in breast milk.]

6. Pediatric Use

The safety of ARICEPT Oral Jelly in children has not been established (no clinical experience).

7. Overdosage

(1) Signs and symptoms

Overdosage of cholinesterase inhibitors may result in cholinergic adverse reactions such as severe nausea, vomiting, salivation, diaphoresis, bradycardia, hypotension, respiratory suppression, collapse and convulsions. Muscle weakness is possible, which may result in death if respiratory muscle is relaxed.

(2) Treatment

Tertiary anticholinergics such as atropine sulfate hydrate may be used as an antidote for overdosage of ARICEPT Oral Jelly. Intravenous atropine sulfate hydrate may be titrated to effect: an initial dose of 1.0 to 2.0 mg i.v. with subsequent doses based upon clinical response.

Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when coadministered with quaternary anticholinergics. It is not known whether ARICEPT Oral Jelly and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

8. Precautions concerning Use

(1) Route of administration

Internal use only

(2) Precautions regarding dispensing

1) Instruct patients or their caregivers to open the aluminum package just before use. (Active ingredient may be degraded by oxidation reaction.)

2) Instruct patients and their caregivers that this drug must not be taken together with the package or cup.

(3) Precautions regarding oral administration

1) This product is a jelly-form drug contained in a cup. Caregivers should divide ARICEPT Oral Jelly into small portions with a spoon before administration to the patient.

2) Use promptly after removing the lid from the cup.

9. Other Precautions

(1) In other countries, three randomized double-blind placebo-controlled clinical trials of 6 months duration were conducted in individuals who met the NINDS-AIREN criteria for probable or possible vascular dementia (VaD) [this indication is not approved in JAPAN] and patients with a diagnosis of Alzheimer's disease were excluded.

In the first study, the mortality rates were 1.0% (2/198) for donepezil hydrochloride 5mg, 2.4% (5/206) for donepezil hydrochloride 10mg and 3.5% (7/199) for placebo. In the second study, the mortality rates were 1.9% (4/208) for donepezil hydrochloride 5mg, 1.4% (3/215) for donepezil hydrochloride 10mg and 0.5% (1/193) for placebo. In the third study, the mortality rates were 1.7% (11/648) for donepezil hydrochloride

5mg and 0% (0/326) for placebo and this difference was statistically significant.

The overall mortality rates for the three VaD studies were 1.7% in the donepezil hydrochloride group (5mg and 10mg) and 1.1% for placebo group, but this difference was not statistically significant.

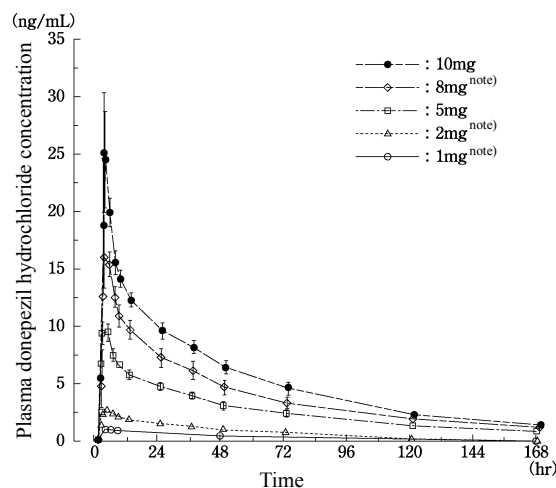
(2) Respiratory suppression resulting in death has been reported with donepezil hydrochloride in dogs anesthetized with ketamine-pentobarbital or pentobarbital.

PHARMACOKINETICS

1. Blood concentration

(1) Single-dose study

The changes over time in the mean plasma donepezil hydrochloride concentration when ARICEPT Tablets were administered orally to healthy adult male volunteers in a single dose during fasting were as shown in the figure below. The peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased dose-dependently. The pharmacokinetic parameters at a dose of 5 mg/10 mg were as shown in the table.



Mean plasma donepezil hydrochloride concentrations after single oral administration to healthy adult male volunteers (tablets)
(Mean \pm S.E., n=6)

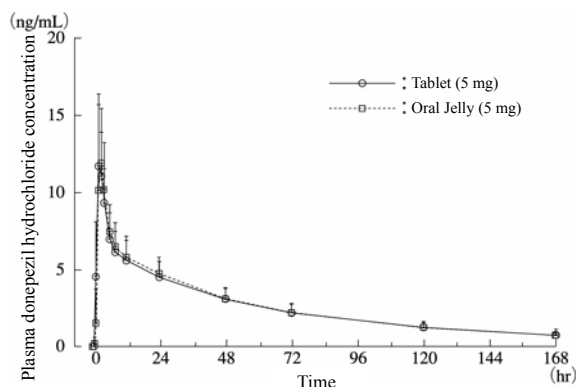
Pharmacokinetic parameters after oral administration to healthy adult male volunteers in a single dose of 5 mg or 10 mg (tablets)

Dose	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng · hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)
5 mg	9.97 \pm 2.08	3.00 \pm 1.10	591.72 \pm 155.87	89.3 \pm 36.0	0.141 \pm 0.040
10 mg	28.09 \pm 9.81	2.42 \pm 1.24	1098.40 \pm 304.63	75.7 \pm 17.3	0.153 \pm 0.043

CL/F : Total clearance

(Mean \pm S.D., n=6)

The changes over time in the mean plasma donepezil hydrochloride concentration when ARICEPT Oral Jelly and ARICEPT Tablet (each dose was 5 mg) were administered orally to healthy adult male volunteers in a single dose during fasting were as shown in the figure below.



Mean plasma donepezil hydrochloride concentrations after single oral administration to healthy adult male volunteers (oral jelly or tablet) (Mean±S.D., n=9)

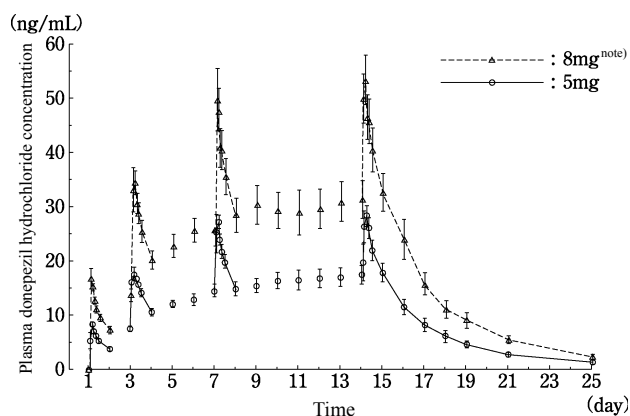
Pharmacokinetic parameters after oral administration to healthy adult male volunteers in a single dose of 5 mg (oral jelly or tablet)

Dose	C _{max} (ng/mL)	t _{max} (hr)	AUC ₀₋₁₆₈ (ng · hr/mL)	t _{1/2} (hr)
Oral Jelly 5 mg	12.70 ±3.90	3.0 (2.0-4.0)	442.7 ±102.8	62.2 ±4.9
Tablet 5 mg	12.25 ±4.13	2.0 (2.0-3.0)	433.4 ±107.4	64.3 ±12.7

(Mean ± S.D., t_{max}: median value (minimum value – maximum value), n=9)

(2) Multiple-dose study

ARICEPT Tablets were administered orally to healthy adult male volunteers once daily at doses of 5 mg and 8mg^{note)} for 14 consecutive days. The plasma concentrations after consecutive administration reached a steady state at 2 weeks after administration and there were considered to be no accumulation and no changes in pharmacokinetic parameters, as shown in the figure below.



Mean plasma donepezil hydrochloride concentration after oral administration to healthy adult male volunteers at doses of 5 mg or 8 mg^{note)} for 14 consecutive days (tablet) (Mean ± S.E., n=6)

(3) Effect of food

The influence of food on the absorption of ARICEPT at a dose of 2mg^{note)} (tablet) was studied in healthy adult male volunteers. The plasma concentration after post-prandial administration was comparable to that during fasting. Thus no influence of food was detected.

(4) Bioequivalence

The bioequivalence of two different dosage forms of ARICEPT Tablet 3 mg and ARICEPT Oral Jelly 3 mg (in 8 healthy adult male volunteers); ARICEPT Tablet 5 mg and ARICEPT Oral Jelly 5 mg (in 9 healthy adult male volunteers), was confirmed. Moreover, ARICEPT Oral Jelly 10 mg was considered to be equal in bioequivalence to that of ARICEPT Tablet 10 mg.

2. Protein binding

Human plasma protein binding *in vitro* was 88.9% and human serum protein binding *in vivo* was 92.6%.

3. Metabolism

It is believed that the main metabolic route of ARICEPT is N-dealkylation and the secondary route is O-demethylation resulting in glucuronide conjugation.

Studies have suggested that N-dealkylation is mainly by CYP3A4 and O-demethylation is mainly by CYP2D6.¹⁾

4. Excretion

When ARICEPT was administered orally to healthy adult male volunteers at a single dose of 2 mg^{note)} (tablet), over 7 days 9.4% of the administered dose was excreted in urine as unchanged drug and including metabolites 29.6% was excreted. Also, the amounts of excretion of the unchanged drug within 11 days after single oral administration of 10mg^{note)} (tablet) were 10.6% in the urine and 1.7% in the feces. Total excretion of the unchanged drug and metabolites in the urine was 35.9% and in the feces it was 8.4%.

5. Pharmacokinetics in elderly patients, patients with liver disease and patients with renal function disorders

(1) Elderly patients

After a single oral administration of 2 mg^{note)} (tablet), when the pharmacokinetic parameters in elderly patients were compared with those in healthy adults, the elimination half life in elderly patients was significantly longer (1.5 times) than that in healthy adults, but no significant differences in C_{max}, t_{max} or AUC were detected.

(2) Patients with liver disease

After a single oral administration of 5 mg (tablet), when the pharmacokinetic parameters in patients with alcoholic liver cirrhosis were compared with those in healthy adults in a US study, the C_{max} in patients with liver disease was significantly higher (1.4 times) than that in healthy adults, but no significant differences in other parameters were detected.²⁾

(3) Patients with renal function disorders

After a single oral administration of 5 mg (tablet), when the pharmacokinetic parameters in patients with renal function disorders were compared with those in healthy adults in a UK study, no significant differences in parameters were detected.³⁾

Note) Approved dosage and administration is as follows. The usual initial adult dose for oral use is 3 mg of donepezil hydrochloride once daily. After 1 to 2 weeks the dosage is increased to 5 mg. The

dosage for patients with severe dementia of Alzheimer type is increased to 10 mg after dosing at 5mg for 4 or more weeks. Dose should be adjusted appropriately according to patient's symptoms.

CLINICAL STUDIES

1. In mild to moderate dementia of the Alzheimer's type.

5 mg of ARICEPT (at a dose of 5mg (tablet)/day for 23 weeks after administration at a dose of 3 mg (tablet)/day for 1 week) or placebo was administered to 268 patients with mild to moderate dementia of the Alzheimer's type for 24 weeks in a double-blind clinical trial.

The ARICEPT 5 mg group was significantly superior to the placebo group in the final global clinical improvement rating. The rates for patients evaluated as "improved" or better were 17% and 13% for the 5 mg group and the placebo group, respectively. Also, the rates for patients evaluated as "slightly aggravated" or worse were 17% and 43% for the 5 mg group and the placebo group, respectively.

Comparison for final clinical global impression of change

Rating		1	2	3	4	5	6	7	8	Total
		Treatment								
5mg	Patients	1	19	40	36	15	4	0	1	116
	%	(1)	(16)	(34)	(31)	(13)	(3)	(0)	(1)	
	Group %	(17)		(34)	(31)	(17)				
Placebo	Patients	1	13	10	40	21	21	5	1	112
	%	(1)	(12)	(9)	(36)	(19)	(19)	(4)	(1)	
	Group %	(13)		(9)	(36)	(43)				

Rating scale

- | | |
|-----------------------|-------------------------|
| 1 : Markedly improved | 5 : Slightly aggravated |
| 2 : Improved | 6 : Aggravated |
| 3 : Slightly improved | 7 : Markedly aggravated |
| 4 : No change | 8 : Unassessable |

The mean change in the Japanese version of the Alzheimer's disease assessment scale-cognitive subscale (ADAS-J cog) score, which indicates cognitive function, is shown in the table (final analyzed cases: 205 patients). The improvement in ADAS-J cog scores from initial administration in the ARICEPT 5 mg group was significantly greater than that in the placebo group from 12 weeks after administration. The difference between the mean change in ADAS-J cog scores before and after administration of 5 mg group and placebo group on final evaluation was 2.44 points.

Mean change in ADAS-J cog scores

Evaluation period	Treatment	Mean change in scores from 0 week ^{note1)}	Comparison of mean change in scores
		Mean±S.E.(n)	Difference between mean change in scores ^{note2)}
12 weeks	5 mg	-3.03±0.47(106)	—
	Placebo	-0.84±0.50(101)	2.19
24 weeks	5 mg	-3.07±0.50(96)	—
	Placebo	-0.11±0.56(86)	2.96
Final ^{note3)}	5 mg	-2.70±0.48(107)	—
	Placebo	-0.26±0.52(98)	2.44

(Negative value indicates improvement.)

The mean change in CDR (clinical dementia rating) score, a severity rating scale, is as shown in the table (final analyzed cases: 228 patients). The mean change in CDR scores

from initial administration was significantly greater in the ARICEPT 5 mg group than that in the placebo group from 12 weeks after administration.⁴⁾

Mean change in CDR scores

Evaluation period	Treatment	Mean change in scores from 0 week ^{note1)}	Comparison of mean change in scores
		Mean±S.E.(n)	Difference between mean change in scores ^{note2)}
12 weeks	5 mg	-0.12±0.08(113)	—
	Placebo	0.23±0.10(109)	0.35
24 weeks	5 mg	-0.14±0.13(104)	—
	Placebo	0.72±0.17(95)	0.86
Final ^{note3)}	5 mg	-0.10±0.12(116)	—
	Placebo	0.75±0.15(112)	0.85

(Negative value indicates improvement.)

Note 1) [Scores in evaluation period] - [scores at 0 week]

Note 2) [Mean change in scores of placebo group from 0 week] - [Mean change in scores of 5mg group from 0 week]

Note 3) In principle, the evaluation score at 24 weeks was used as the final score. For discontinued or dropout patients, final scores at 12 or more weeks were counted as analyzed cases.

2. Severe dementia of the Alzheimer's type

10 mg of ARICEPT (at a dose of 10 mg (tablet)/day for 18 weeks after administration at a dose of 3 mg (tablet)/day for 2 weeks and 5 mg (tablet)/day for 4 weeks) or 5 mg of ARICEPT (at a dose of 5 mg (tablet)/day for 22 weeks after administration at a dose of 3 mg (tablet)/day for 2 weeks) or placebo was administered to 302 patients with severe dementia of the Alzheimer's type for 24 weeks in a double-blind clinical trial.

The ARICEPT 10 mg group was significantly superior to the placebo group according to CIBIC-plus (Clinician's Interview-based Impression of Change Plus Caregiver Assessment).

(final analyzed cases: 287 patients).

CIBIC plus at final period

Rating		1	2	3	4	5	6	7	8	Total
		Treatment								
10mg	Patients	0	7	35	20	19	9	0	0	90
	%	(0)	(8)	(39)	(22)	(21)	(10)	(0)	(0)	
5mg	Patients	0	4	27	26	30	9	0	0	96
	%	(0)	(4)	(28)	(27)	(31)	(9)	(0)	(0)	
Placebo	Patients	0	6	18	30	34	11	1	1	101
	%	(0)	(6)	(18)	(30)	(34)	(11)	(1)	(1)	

Rating scale

- | | |
|-----------------------|-------------------------|
| 1 : Markedly improved | 5 : Slightly aggravated |
| 2 : Improved | 6 : Aggravated |
| 3 : Slightly improved | 7 : Markedly aggravated |
| 4 : No change | 8 : Unassessable |

The final change in the SIB score, which indicates cognitive function, is shown in the table (final analyzed cases: 288 patients). The difference between the mean change in SIB scores before and after administration was significantly greater in the ARICEPT 5 mg group and 10 mg group than that in the placebo group, which were 6.7 and 9.0 respectively.⁵⁾

SIB scores at final period^{note1)}

Treatment	Mean change in scores from 0 week ^{note2)}	Comparison of mean change in scores
	Mean±S.E. (n)	Difference between mean change in scores ^{note3)}
10 mg	4.7±1.1 (92)	9.0
5 mg	2.5±1.0 (95)	6.7
Placebo	-4.2±1.0(101)	-

(Positive value indicates improvement.)

Note 1) In principle, the evaluation score at 24 weeks was used as the final score. For discontinued or dropout patients, final scores were counted as analyzed cases.

Note 2) [Final scores] – [scores at 0 week]

Note 3) [Mean change in scores of each treatment group from 0 week] – [Mean change in scores of placebo group from 0 week]

PHARMACOLOGY

1. Mechanism of action

In dementia of the Alzheimer's type marked disorders of the cerebral cholinergic nervous system have been observed. Donepezil hydrochloride increases cerebral acetylcholine (ACh) due to its reversible inhibition of acetylcholinesterase (AChE), the enzyme metabolizing acetylcholine, thereby activating the cerebral cholinergic nervous system.⁶⁻⁹⁾

2. Inhibition of AChE and selectivity of AChE

Donepezil hydrochloride's IC₅₀ for AChE inhibitory effect *in vitro* was 6.7 nmol/L and IC₅₀ for butyrylcholinesterase inhibitory effect *in vitro* was 7,400 nmol/L. Donepezil hydrochloride showed a selective inhibitory effect.⁶⁾

3. Cerebral AChE inhibitory effect and increase in ACh

When donepezil hydrochloride was administered orally to rats, it inhibited cerebral AChE and increased cerebral ACh.^{7, 8)}

4. Improvement of impaired learning function

When donepezil hydrochloride was administered orally in a model of cerebral cholinergic nervous system hypofunction (rats with impaired learning due to medial septal lesions), it improved the impaired learning function.⁹⁾

PHYSICOCHEMISTRY

Nonproprietary name: Donepezil Hydrochloride

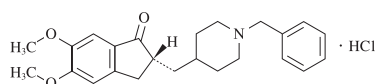
Chemical name:

(2*RS*)-2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one monohydrochloride

Molecular formula: C₂₄H₂₉NO₃ · HCl

Molecular weight: 415.95

Structural formula:



And enantiomer

Description:

Donepezil hydrochloride occurs as a white crystalline powder. It is soluble in water, slightly soluble in ethanol (99.5).

It shows no optical rotation.

Melting point: 223.5°C (decomposition)

Partition coefficient: log P=4.27 (1-octanol/water)

PRECAUTIONS FOR HANDLING

1. To avoid misuse, do not transfer ARICEPT Oral Jelly to another container or item of tableware for storage.
2. Keep out of reach of children.
3. Protect from high temperatures.
4. Pay attention to the explanatory notes on the package, and do not keep ARICEPT Oral Jelly the wrong side up.
5. Keep ARICEPT Oral Jelly in the aluminum package throughout storage. (An oxygen absorber is enclosed in the aluminum package.)
6. Some liquid separation from the jelly may be observed on its surface.

PACKAGING

ARICEPT Oral Jelly 3 mg:

Boxes of 14 (7 cups × 2)

ARICEPT Oral Jelly 5 mg:

Boxes of 14 (7 cups × 2)

ARICEPT Oral Jelly 10 mg:

Boxes of 14 (7 cups × 2)

REFERENCES

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REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

Drug Information Center

Fax: 03-3379-3053

Pfizer Japan Inc.

**REQUEST FOR PRODUCT INFORMATION SHOULD
BE MADE TO:**

Customer Information Service
Free Dial: 0120-419-497
Eisai Co., Ltd.

Drug Information Center
Toll Free: 0120-664-467
Pfizer Japan Inc.

Manufactured and marketed by:

Eisai Co., Ltd.
6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088

Marketed by:

Pfizer Japan Inc.
3-22-7, Yoyogi, Shibuya-ku, Tokyo, 151-8589 JAPAN