1. TRADE NAME OF THE MEDICINAL PRODUCT

ARICEPT® 5 mg (donepezil hydrochloride)
ARICEPT® 10 mg (donepezil hydrochloride)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg donepezil hydrochloride tablets each containing 4.56 mg donepezil free base
10 mg donepezil hydrochloride tablets each containing 9.12 mg donepezil free base

3. PHARMACEUTICAL FORM

Film-Coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

ARICEPT tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.
Special warnings and precautions for use in this indication may be found in Section 4.4.

4.2 Posology and method of administration

Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). ARICEPT should be taken orally, in the evening, just prior to retiring. The 5 mg/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 one-month clinical assessment of treatment at 5 mg/day, the dose of ARICEPT can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.
Duration of treatment has not been investigated in placebo-controlled trials beyond 6 months. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of ARICEPT is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.
Renal and hepatic impairment:
A similar dose schedule can be followed for patients with renal or mild to moderate hepatic impairment as clearance of donepezil hydrochloride is not affected by these conditions.
Children:
ARICEPT is not recommended for use in children.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

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 (e.g. DSM IV, ICD 10). 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 exists.
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. The use of ARICEPT in patients with severe Alzheimer's dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.
Anaesthesia: ARICEPT, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.
Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.
Gastrointestinal Conditions: Patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with ARICEPT showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.
Genitourinary: Although not observed in clinical trials of ARICEPT, cholinomimetics may cause bladder outflow obstruction.
Neurological Conditions: Seizures: 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 ARICEPT concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

4.5 Interaction with other medicaments and other forms of interaction

The clinical experience with donepezil is presently limited. For this reason, it may be possible that all possible interactions have not been recorded. The prescribing physician should be aware of the possibility of new, as yet unknown interactions with donepezil.
Donepezil hydrochloride and/or any of its metabolites does not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 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%. 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 combinations 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 medications such as succinylcholine, other neuromuscular blo-cking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction.

4.6 Pregnancy and lactation

Pregnancy:

Teratology studies conducted in pregnant rats at doses up to approximately 80 times the human dose and in pregnant rabbits at doses up to approximately 50 times the human dose did not disclose any evidence for a teratogenic potential. However, in a study in which pregnant rats were given approximately 50 times the human dose from day 17 of gestation through day 20 postpartum, there was a slight increase in stillbirths and a slight decrease in pup survival through day 4 postpartum. No effect was observed at the next lower dose tested, approximately 15 times the human dose.

ARICEPT should not be used during pregnancy.

Lactation:

It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Therefore, women on donepezil should not breast feed.

4.7 Effects on ability to drive and use machines

Alzheimer's Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, donepezil can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The ability of Alzheimer patients on donepezil to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

The most common adverse events (incidence ≥ 5% and twice the frequency of placebo) were diarrhoea, 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.

Rare cases of syncope, bradycardia, sinoatrial block and atrio-ventricular block were observed.

No notable abnormalities in laboratory values were observed, except for minor increases in serum concentrations of muscle creatine kinase.

4.9 Overdose

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice and rats is 45 and 32 mg/kg, respectively, or approximately 225 and 160 times the maximum recommended human dose of 10 mg per day. Dose-related signs of cholinergic stimulation were observed in animals and included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation and lower body surface temperature.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT overdosage. Intravenous atropine sulphate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of ARICEPT

produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correlate to changes in ADAS-cog, a sensitive scale which examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus ARICEPT can not be considered to have any effect on the progress of the disease.

In the clinical trials, an analysis was done at the conclusion of 6 months of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

	% Réponse	
	Intent to Treat Population n=365	Evaluable Population n=352
Placebo Group	10%	10%
Aricept 5-mg Group	18%*	18%*
Aricept 10-mg Group	21%*	22%**

*p<0.05
**p<0.01

ARICEPT produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

5.2 Pharmacokinetic properties - General Characteristics

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. Approximate steady-state is achieved within 3 weeks after initiation of therapy. Once at steady-state, plasma donepezil hydrochloride concentrations and the related pharmacodynamic activity show little variability over the course of the day. Food did 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 in 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 5 mg dose of 14C-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 hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of 14C-labeled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%, 6-O-desmethyl donepezil (11% - only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%) and the glucoronide conjugate of 5-O-desmethyl donepezil (3%).

Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

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 patients. However mean plasma levels in patients closely agreed with those of young healthy volunteers.

5.3 Preclinical Safety Data

Extensive testing in experimental animals has demonstrated that this compound causes few effects other than the intended pharmacological effects consistent with its action as a cholinergic stimulator (see Section 4.9 above). Donepezil is not mutagenic in bacterial and mammalian cell mutation assays. Some clastogenic effects were observed in vitro at concentrations overtly toxic to the cells and more than 3000 times the steady-state plasma concentrations. No clastogenic or other genotoxic effects were observed in the mouse micronucleus model in vivo. Data regarding carcinogenic potential are not yet available.

Donepezil hydrochloride had no effect on fertility in rats, and was not teratogenic in rats or rabbits, but had a slight effect on still births and early pup survival when administered to pregnant rats at 50 times the human dose (see Section 4.6 above).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hypromellose and titanium dioxide. Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a colouring agent.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

5 mg tablets:
28 tablets in blister strips (PVC/Alu. foil)
10 mg tablets:
28 tablets in blister strips (PVC/Alu. foil)

6.6 Instructions for use/handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Eisai S.A., Tour Manhattan - La Défense 2
5/6, place de l'Iris
92 095 PARIS LA DEFENSE

8. MARKETING AUTHORISATION NUMBER

344 490-9 (5 mg)
344 495-0 (10 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF TI AUTHORISATION

03 September 1997

10. DATE OF (PARTIAL) REVISION OF THE TEXT

03 September 1997

Manufactured by:

Pfizer, Amboise, France

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