SP 407

# Aricept® Evess *Orodispersible Tablets* 5 mg, 10 mg

*Donepezil Hydrochloride*

# Aricept® *Film-Coated Tablets* 23 mg

*Donepezil Hydrochloride*

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**1. TRADE NAME OF THE MEDICINAL PRODUCT**

ARICEPT® EVESS Orodispersible Tablets 5 mg (donepezil hydrochloride)
ARICEPT® EVESS Orodispersible Tablets 10 mg (donepezil hydrochloride)
ARICEPT® Film-coated Tablets 23 mg (donepezil hydrochloride)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

ARICEPT® EVESS Orodispersible Tablets 5 mg each containing 4.56 mg donepezil free base
ARICEPT® EVESS Orodispersible Tablets 10 mg each containing 9.12 mg donepezil free base
ARICEPT® Film-coated Tablets 23 mg each containing 20.98 mg donepezil free base
For excipients, see 6.1

**3. PHARMACEUTICAL FORM**

**Orodispersible tablets**
5mg: White tablet debossed with "5" on one side and "Aricept" on the other side.
10mg: Yellow tablet debossed with "10" on one side and "Aricept" on the other side.
**Film-coated tablets**
23mg Reddish tablet debossed with "23" on one side and "Aricept" on the other side.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indication**

ARICEPT® is indicated for the symptomatic treatment of mild to moderate and severe Alzheimer's dementia. ARICEPT® Film-coated Tablet 23mg should only be administered to patients whose condition is not adequately controlled by a lower dose of donepezil hydrochloride 10mg.

**4.2 Posology and method of administration**

**Adults/Elderly:**
Treatment is initiated at 5 mg/day (once-a-day dosing). 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 4-6 weeks clinical assessment of treatment at 5 mg/day, the dose of ARICEPT® can be increased to 10 mg/day (once-a-day dosing). If well tolerated and after being stabilized on a daily dose of 10 mg for at least 3 months, the dose may be increased to 23mg (given as one ARICEPT® Film-coated Tablet 23 mg) once daily in patients whose condition is not adequately controlled. ARICEPT® EVESS Tablets should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. ARICEPT® Film-coated Tablets can be taken once daily in the evening just prior to retiring and can be taken with or without food. ARICEPT® Film-coated Tablets 23 mg should not be split or crushed and should be swallowed whole with water.
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 impairment as clearance of donepezil hydrochloride is not affected by this condition.
Due to possible increased exposure in mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.
**Children:**
ARICEPT® is not recommended for use in children.

**4.3 Contraindications**

ARICEPT® is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine 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 by a physician experienced in the treatment of dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil hydrochloride should only be started if a care-giver 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 hydrochloride 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 hydrochloride cannot be predicted. The use of ARICEPT® in patients with 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 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 ARICEPT® Film-coated Tablets 23 mg. There have been post marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.
***Nausea and Vomiting:*** 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/day dose than with the 10 mg/day 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 hydrochloride 10 mg/day for at least three months, the incidence of nausea in the 23 mg/day dose group was markedly greater than in the patients who continued on 10 mg/day dose (11.8% vs 3.4%, respectively), and the incidence of vomiting in the 23 mg/day dose group was markedly greater than in the 10 mg/day dose group (9.2% vs 2.5%, respectively). The percentage of patients who discontinued treatment due to vomiting in the 23 mg/day dose group was markedly higher than in the 10 mg/day dose 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.
***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 non-steroidal anti-inflammatory drugs (NSAIDS). Results of a controlled clinical study of ARICEPT® Film-coated Tablets 23 mg 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%).
***Weight Loss:*** Weight loss was reported as an adverse event, in 4.7% of patients assigned to ARICEPT® Film-coated Tablets 23 mg compared to 2.5% of patients assigned to 10 mg donepezil hydrochloride. Compared to their baseline weights, 8.4% of patients in the ARICEPT® Film-coated Tablets 23 mg group were found to have a weight decrease of ≥ 7% by the end of the study, while 4.9% of the group taking 10 mg donepezil hydrochloride were found to have a weight loss of ≥ 7% at the end of the study.
***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. Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.
***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.
***Severe Hepatic Impairment:*** There are no data for patients with severe hepatic impairment.
***Neurologic:*** Neuroleptic Malignant Syndrome (NMS): There have been very rare post-marketing reports of Neuroleptic Malignant Syndrome (NMS) in patients treated with ARICEPT with or without concomitant antipsychotic medication. NMS is a potentially life-threatening condition characterized by hyperthermia, muscle rigidity, autonomic instability (e.g. irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia), altered consciousness and elevated serum creatine phosphokinase (CPK) levels. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever in the absence of additional clinical manifestations of NMS, ARICEPT therapy should be discontinued.
***Rhabdomyolysis (Muscle Effects):*** Rare cases of rhabdomyolysis (including acute renal failure) have been reported in patients treated with ARICEPT, particularly in the days following dose initiation and dose increase. Majority of these cases occurred independently of Neuroleptic Malignant Syndrome (NMS). Patients should be carefully monitored for muscle pain, tenderness or weakness and darkened urine, particularly if accompanied by malaise or fever. Blood creatine phosphokinase (CPK) levels should be assessed in patients experiencing these symptoms. ARICEPT therapy should be discontinued if markedly elevated CPK levels are measured and/or if the patient develops signs and symptoms indicative of rhabdomyolysis.
Although the decision to discontinue ARICEPT should be made based on the clinical judgement of the treating physician, in most post-marketing cases, therapy was withdrawn when CPK levels were 5X upper limit of normal or higher. Caution should be particularly exercised in prescribing ARICEPT to patients with predisposing/risk factors such as prior history of muscular disorders, uncontrolled hypothyroidism, hepatic or renal impairment, and in patients who are receiving concomitant medications that can cause rhabdomyolysis (e.g., statins, antipsychotics, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor).

**4.5 Interaction with other medicinal products and other forms of interaction**

**Effect of ARICEPT® 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 CYP3A4 (e.g. cisapride, terfenadine) or by CYP2D6 (e.g. imipramine). However, in vitro studies show a low rate of binding to these enzymes (mean Ki about 50-130μM), that, given the therapeutic plasma concentrations of donepezil hydrochloride (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of donepezil hydrochloride for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effe cts on the pharmacokinetics of these drugs were observed.
**Effect of Other Drugs on the Metabolism of ARICEPT®**
Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil hydrochloride metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil hydrochloride (5 mg q.d.) concentrations (AUC0-24 and Cmax) by 36%. The clinical relevance of this increase in concentration is unknown.
A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil hydrochloride concentrations measured in patients with Alzheimer's disease. Donepezil hydrochloride 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 hydrochloride.
Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic studies demonstrated that the metabolism of donepezil hydrochloride is not significantly affected by concurrent administration of digoxin or cimetidine.
**Use with Anticholinergics**
Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.
**Use with Cholinomimetics and Other Cholinesterase Inhibitors**
A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuro-muscular blocking agents or cholinergic agonists such as bethanechol.
**Use with other medicinal products known to prolong QTc interval**
Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:
- Class IA antiarrhythmics (e.g. quinidine)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)

**4.6 Use in Specific Population**

**Pregnancy:**
Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Oral administration of donepezil hydrochloride to pregnant rats and rabbits during the period of organogenesis did not produce any teratogenic effects at doses up to 16 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m$^2$ basis) and 10 mg/kg/day (approximately 7 times the MRHD on a mg/m$^2$ basis), respectively. Oral administration of donepezil hydrochloride (1, 3, 10 mg/kg /day) to rats during late gestation and throughout lactation to weaning produced an increase in stillbirths and reduced offspring survival through postpartum day 4 at the highest dose. The no-effect dose of 3 mg/kg/day is approximately equal to the MRHD on a mg/m$^2$ basis.
**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 hydrochloride should not breast feed.
**Pediatric Use**
The safety and effectiveness of ARICEPT® in children have not been established.
**Geriatric Use**
Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical study with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old, and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old.
**Lower Weight Individuals**
In the controlled clinical trial, among patients in the ARICEPT® Film- coated Tablets 23 mg treatment group, those weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse events as well. This finding may be related to higher plasma exposure associated with lower weight.

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
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, <1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data).

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not Known |
|---|---|---|---|---|---|---|
| Infections and infestations | | Common cold | | | | |
| Metabolism and nutrition disorders | | Anorexia | | | | |
| Psychiatric disorders | | Halluci-nations** Agitation** Aggressive behavior** Abnormal dreams and Nightmares** | | | | |
| Nervous system disorders | | Syncope* Dizziness Insomnia | Seizure*, | Extrapyra-midal symptoms, (NMS) | Neuroleptic Malignant Syndrome | |
| Cardiac disorders | | | Bradycardia | Sino-atrial block Atrioven-tricular block | | Polymorphic ventricular tachycardia including Torsade de Pointes Electrocardio gram QT interval prolonged |
| Gastrointes tinal disorders | Diarrhoea Nausea | Vomiting Abdominal disturbance | Gastroin testinal haemor rhage Gastric and duodenal ulcers Salivary hypersec retion | | | |
| Hepato-biliary disorders | | | | Liver dysfunction including hepati tis*** | | |
| Skin and subcutaneous tissue disorders | | Rash Pruritis | | | | |
| Musculos keletal, connective tissue and bone disorders | | Muscle cramps | | | Rhabdomy-olysis**** | |
| Renal and urinary | | Urinary incontinence | | | | |
| General disorders and administration | Headache | Fatigue Pain | | | | |
| Investigations | | | Minor increase in serum concen tration of muscle creatine kinase | | | |
| Injury and poisoning | | Accidents including falls | | | | |

*In investigating patients for syncope or seizure, the possibility of heart block or long sinusal pauses should be considered (see section 4.4)
**Reports of hallucinations, agitation and aggressive behavior have resolved on dose-reduction or discontinuation of treatment.
***In cases of unexplained liver dysfunction, withdrawal of ARICEPT® should be considered.

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**** Rhabdomyolysis has been reported to occur independently of Neuroleptic Malignant syndrome and in close temporal association with donepezil initiation or dose increase.

**Adverse Events Leading to Discontinuation**

The rate of discontinuation from a controlled clinical trial of ARICEPT® Film-coated Tablets 23 mg due to adverse events was higher (18.6%) than for the donepezil hydrochloride 10 mg/day treatment group (7.9%).

The most common adverse events leading to discontinuation, defined as those occurring in at least 1% of patients and greater than those occurring with donepezil hydrochloride 10 mg/day doses, are shown in Table 1:

Table 1. Most Frequent Adverse Events Leading to Discontinuation from a Controlled Clinical Trial by Treatment Group

| Dose Group | 23 mg/day ARICEPT® | 10 mg/day ARICEPT® |
|---|---|---|
| Safety Population | 963 | 471 |
| Event/ % Discontinuing | | |
| Vomiting | 3 | 0 |
| Diarrhea | 2 | 0 |
| Nausea | 2 | 0 |
| Dizziness | 1 | 0 |

The majority of discontinuations due to adverse events in the ARICEPT® Film-coated Tablets 23 mg group occurred during the first month of treatment.

**Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® Film-coated Tablets 23 mg**

The most common adverse events, defined as those occurring at a frequency of at least 5%, include nausea, diarrhea, vomiting, and anorexia. These adverse events were often of mild to moderate intensity.

**Adverse Events Reported in Controlled Trials**

The events cited reflect experience gained under closely monitored conditions of a controlled clinical trial in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the lands of patients treated may differ. Table 2 lists adverse events that were reported in at least 2% of patients who received 23 mg/day of ARICEPT® and at a higher frequency than those receiving 10 mg/day of ARICEPT® in a controlled clinical trial that compared the two doses. In this study, there were no important differences in the type of adverse events in patients taking ARICEPT® with or without memantine.

Table 2. Adverse Events Reported in a Controlled Clinical Trial in Moderate to Severe Alzheimer's Disease in at Least 2% of Patients and Higher in the 23 mg/day Group

| Body System/Adverse Event | 23 mg/day ARICEPT® | 10 mg/day ARICEPT® |
|---|---|---|
| Safety Population | 963 | 471 |
| Percent of Patients with any Adverse Event | 74 | 64 |
| Gastrointestinal disorders | | |
| Nausea | 12 | 3 |
| Vomiting | 9 | 3 |
| Diarrhea | 8 | 5 |
| General disorders and administration site conditions | | |
| Fatigue | 2 | 1 |
| Asthenia | 2 | 1 |
| Injury, poisoning and procedural complications | | |
| Confusion | 2 | 0 |
| Investigations | | |
| Weight, decrease | 5 | 3 |
| Metabolism and nutrition disorders | | |
| Anorexia | 5 | 2 |
| Nervous system | | |
| Dizziness | 5 | 3 |
| Headache | 4 | 3 |
| Somnolence | 2 | 1 |
| Psychiatric disorders | | |
| Insomnia | 3 | 2 |
| Renal and urinary disorders | | |
| Urinary incontinence | 3 | 1 |

**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, stagger¬ing gait, lacrimation, clonic convulsions, depressed respiration, sali¬vation, miosis, fasciculation and lower body surface temperature. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweat¬ing, 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 anti¬cholinergics 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**

The 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 *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.

**Clinical trials**

**Mild to Moderately Severe Alzheimer's disease**

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 acetyl-cholinesterase (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 donepezil hydrochloride (ARICEPT®) cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer's dementia with ARICEPT® has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration. In the 6-month clinical trial, an analysis was done at the conclusion of donepezil hydrochloride 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

| | % Response | |
|---|---|---|
| | 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.

**Severe Alzheimer's disease**

Efficacy of treatment with ARICEPT® 10mg in severe Alzheimer's disease has been investigated in three placebo-controlled trials of 6-month duration. In each of the clinical trials, an analysis was done at the conclusion of donepezil hydrochloride treatment using a combination of three efficacy criteria: the total Severe Impairment Battery (SIB – a measure of cognitive performance in all three trials) score, the Clinician's Interview Based Impression of Change with caregiver input (CIBIC+ - a measure of global function in two trials) or Clinical Global Impression of Change (CGI-I – a measure of global function in one trial) and the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory for severe Alzheimer's disease (ADCS-ADL-sev – a measure of function in all three trials).

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

Response = Improvement of SIB of at least 4 points
No deterioration of CIBIC+ or CGI-I
No deterioration of ADCS-ADL-sev

| | % Response | |
|---|---|---|
| | Intent to Treat Population n = 571 | Evaluable Population n = 518 |
| Placebo Group | 10% | 10% |
| ARICEPT® 10-mg Group | 29%** | 30%** |

** p<0.001

The effectiveness of ARICEPT® Film-coated Tablets 23 mg as a treatment for moderate to severe Alzheimer's disease compared to donepezil hydrochloride 10 mg has been demonstrated by the results of a randomized, double-blind, controlled clinical investigation in patients with moderate to severe Alzheimer's disease. The controlled clinical study was conducted globally in patients with probable Alzheimer's disease diagnosed by NINCDS-ADRDA and DSM-IV criteria, MMSE: range of 0-20. Patients were required to have been on a stable dose of ARICEPT® 10 mg/day for at least 3 months prior to screening.

One thousand four hundred and thirty four (1434) patients with moderate to severe Alzheimer's disease were randomized to 23 mg/day or 10 mg/day. The mean age of patients was 73.8 years, with a range of 47 to 90. Approximately 63% of patients were women, and 37% were men. Approximately 36% of the patients were taking memantine throughout the study.

**Study Outcome Measures:** The effectiveness of treatment with ARICEPT® Film-coated Tablets 23 mg was determined using a dual outcome assessment strategy that evaluated cognitive function using an instrument designed for more impaired patients and overall function through caregiver-rated assessment. This study showed that patients on ARICEPT® Film-coated Tablets 23 mg Film-coated Tablets 23 mg to improve cognitive performance was assessed with the Severe Impairment Battery (SIB). The SIB, a multi-item instrument, has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB evaluates selective aspects of cognitive performance, including elements of memory, language, orientation, attention, praxis, visuospatial ability, construction, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

The ability of ARICEPT® Film-coated Tablets 23 mg to produce an overall clinical effect was assessed using a Clinician's Interview-Based Impression of Change that incorporated the use of caregiver information, the CIBIC-plus. The CIBIC-plus used in this trial was a semi-structured instrument that examines four major areas of patient function: General, Cognitive, Behavioral and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved" to a score of 4, indicating "no change" to a score of 7, indicating "markedly worse".

**Effects on the SIB:** Figure 1 shows the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the LS mean difference in the SIB change scores for ARICEPT® Film-coated Tablets 23 mg treated patients compared to patients treated with 10 mg donepezil hydrochloride was 2.2 units (p <0.0001). ARICEPT® Film-coated Tablets 23 mg was statistically significantly superior to 10 mg donepezil hydrochloride.

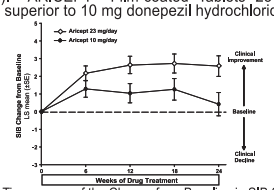


Figure 1. Time-course of the Change from Baseline in SIB Score for Patients Completing 24 Weeks of Treatment.

Figure 2 illustrates the cumulative percentages of patients from each of the twotreatment groups who attained the measure of improvement in SIB score shown on the X-axis. While patients assigned both to ARICEPT® Film-coated Tablets 23 mg and to donepezil hydrochloride 10 mg tablets have a wide range of responses, the curves show that the ARICEPT® Film-coated Tablets 23 mg group is more likely to show a greater improvement in cognitive performance. When such curves are shifted to the left, this indicates a greater percentage of patients responding to treatment on the SIB.

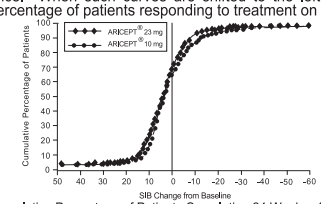


Figure 2. Cumulative Percentage of Patients Completing 24 Weeks of Double- blind Treatment with Specified Changes from Baseline SIB Scores

Effects on the CIBIC-plus:

Figure 3 is a histogram of the frequency distribution of CIBIC-plus scores attained by patients at the end of 24 weeks of treatment. The mean difference between ARICEPT® Film-coated Tablets 23 mg and donepezil hydrochloride 10 mg tablets was 0.06 units. This difference was not statistically significant.

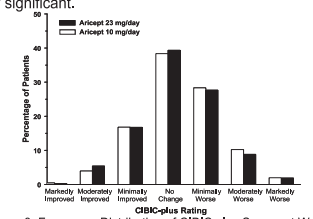


Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24

**5.2 Pharmacokinetic properties - General characteristics**

*Absorption:* Maximum plasma levels are reached approximately 3 to 4 hours after oral administration for ARICEPT® EVESS 5mg and 10mg orodispersible tablets. Based on population pharmacokinetic analysis of plasma donepezil hydrochloride concentrations measured in patients with Alzheimer's disease, following oral dosing, peak plasma concentration is achieved for ARICEPT® Film-coated Tablets 23 mg in approximately 8 hours. Peak plasma concentrations were almost 2-fold higher for ARICEPT® Film-coated Tablets 23 mg than ARICEPT® 10 mg tablets. The elimination half life of donepezil hydrochloride 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 hydrochloride accumulates in plasma by 4-7 fold, and steady state is reached within 15 days. 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:* The steady state volume of distribution is 12-16 L/kg. Donepezil hydrochloride is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha-1-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL. The plasma protein binding of the active metabolite 6-O-desmethyl donepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitive¬ly studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg 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 hydrochloride 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 hydrochloride is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of $^{14}$C-labeled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present, primarily as intact, donepezil hydrochloride (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent, as donepezil hydrochloride in vitro and was found in plasma at concentrations equal to about 20% of donepezil hydrochloride. 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 hydrochloride 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 metabolizes, poor metabolizes 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 hydrochloride.

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

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

Age: No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of ARICEPT®. Population pharmacokinetic analysis suggested that the clearance of donepezil hydrochloride 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 hydrochloride 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 ARICEPT®. However, retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil hydrochloride concentrations measured in patients with Alzheimer's disease indicates that gender and race (Japanese and Caucasians) did not affect the clearance of 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/h 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 hydrochloride 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 hydrochloride to human albumin was not affected by furosemide, digoxin and warfarin.

**5.3 Preclinical safety data**

Extensive testing in experimental animals has demonstrated that this compound causes few effects other than the intended pharmacolo-gical effects consistent with its action as a cholinergic stimulator (See Section 4.9 above). Donepezil hydrochloride 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*.

There was no evidence of oncogenic potential in long term carcino-genicity studies in either rats or mice. No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 40 times the maximum recommended human dose of 23 mg/day on a mg/m$^2$ basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m$^2$ basis). 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**

**Aricept® Evess Orodispersible Tablets 5 mg/10 mg:**
Mannitol
Silica, colloidal anhydrous
K-carrageenan
Polyvinyl alcohol
Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a colouring agent.

**Aricept® Film-coated Tablet 23 mg:**
Ethylcellulose
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate
Methacrylic acid copolymer, Type C
Hypromellose 2010
Iron oxide red
Polyethylene glycol 8000
Talc
Titanium dioxide

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

Aricept® Evess Orodispersible Tablets 5mg/10mg: 36 months
Aricept® Film-coated Tablets 23 mg: 48 months

**6.4 Special precautions for storage**

Do not store above 30ºC.
Tablets may change color with light, so keep in aluminium pouch until taken.

**6.5 Nature and contents of container**

**Aricept® Evess Orodispersible Tablets 5mg/10mg:**
Unit dose blister strips (PVC/PE/PVdC/Aluminium foil) in aluminium pouch
Pack sizes: 28 tablets

**Aricept® Film-coated Tablets 23 mg:**
Unit dose blister strips (PCTFE/PVC/Aluminium foil)
Pack size: 28 tablets

**Not all presentations are marketed in Singapore**

**6.6 Instruction for use/handling**

No special instructions.

## 7. DATE OF REVISION OF THE TEXT

March 2023

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112400210
P5/23 E2/2 (SP)