Aricept® 5mg, 10mg

Donepezil Hydrochloride

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.
87.17 mg lactose/ film-coated tablet
10 mg donepezil hydrochloride tablets each containing 9.12 mg donepezil free base.
174.33 mg lactose/ film-coated tablet
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film-Coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

ARICEPT® tablets are indicated for the symptomatic treatment of:

- Mild, moderately severe and severe dementia of the Alzheimer's type,
- Vascular dementia (dementia associated with cerebrovascular disease),
- Dementia with Lewy bodies (DLB)

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 4-6 weeks of clinical assessment in patients who tolerated treatment at 5mg/day, the dose of ARICEPT can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg for Vascular dementia and DLB. Doses greater than 10 mg/day have not been studied in clinical trials for Vascular dementia and DLB.

For patient with DLB, the dose may be decreased to 5 mg depending on the symptoms of the patient.

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 (see section 5.2), 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
Hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use
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.

There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusal pauses should be considered.

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.

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
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.

Neuroleptic Malignant Syndrome (NMS)

NMS, a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics. 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 without additional clinical manifestations of NMS, treatment should be discontinued.

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.

Mortality in Vascular Dementia Clinical Trials
Three clinical trials of 6 months duration, ie. E2020-307 study (N=404), E2020-308 study (N=423) and E2020-319 study (N=648), 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. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. 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 patients 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.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or, digoxin in humans. The metabolism of donepezil hydrochoride 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 neuro-muscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction.

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 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of donepezil in pregnant women.

Studies in animals have not shown teratogenic effect but have shown pre and post natal toxicity (see section 5.3 preclinical safety data). The potential risk for humans is unknown.

ARICEPT should not be used during pregnancy unless clearly necessary.

Breastfeeding

Donepezil is excreted in the milk of rats. 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

Donepezil has minor to moderate influence on the ability to drive and use machines.

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 treating physician should routinely evaluate the ability of patients on donepezil 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 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data).

Table 1

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations		Common cold				
Metabolism and nutrition disorders		Anorexia				
Psychiatric disorders		Hallucinations** Agitation** Aggressive behaviour** Abnormal dreams and Nightmares**				
Nervous system disorders		Syncope* Dizziness Insomnia	Seizure*	Extrapyramidal symptoms	Neuroleptic malignant syndrome	
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block		Polymorphic ventricular tachycardia including Torsade de Pointes Electrocardiogram QT interval prolonged
Gastrointestinal disorders	Diarrhoea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers Salivary hypersecretion			
Hepato-biliary disorders				Liver dysfunction including hepatitis***		
Skin and subcutaneous tissue disorders		Rash Pruritis				
Musculoskeletal, connective tissue and bone disorders		Muscle cramps			Rhabdomyolysis****	

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
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		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, abnormal dreams, nightmares, agitation and aggressive behaviour have resolved on dose-reduction or discontinuation of treatment.

***In cases of unexplained liver dysfunction, withdrawal of ARICEPT should be considered.

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

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. In the combined vascular dementia studies the mortality rate in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%) (Section 4.4).

Dementia with Lewy Bodies

The safety 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 behavior, seizure, hepatitis, gastric ulcer, duodenal ulcer, and gastrointestinal hemorrhage.

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

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.

Alzheimer's Dementia

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 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 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 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

Table 2

	% 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 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 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

Table 3

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

** p<0.001

Vascular dementia

Efficacy of treatment of Vascular dementia with ARICEPT has been investigated in three placebo-controlled trials of 6-month duration in which the diagnostic criteria for Vascular dementia proposed by the NINDS-AIREN consensus group (National Institute of Neurological Disorders and Stroke-*Association Internationale pour la Recherche et l'Enseignement en Neurosciences*) were used to define the population of patients studied.

An overall analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria.

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

Response = Improvement of ADAS-Cog of at least 4 points *and*
Improvement or no deterioration of CIBIC+ *and*
Improvement or no deterioration of Clinical Dementia Rating functionality subscale

Table 4

	% Response	
	Intent to Treat Population n=1176	Observed Cases n=955
Placebo group	16%	16%
ARICEPT 5-mg group	21%*	22%#
ARICEPT 10-mg group	25%**	27%**

p = 0.052

* p < 0.05

** p < 0.01

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

Dementia with Lewy Bodies

The effectiveness of donepezil hydrochloride as a treatment for Dementia with Lewy Bodies (DLB) was investigated in two multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week studies in Japanese patients diagnosed with probable DLB according to the consensus diagnostic criteria of the 1st Consortium on DLB International Workshop, MMSE: range 10-26.

Japanese Exploratory 12-Week Study

A total of 140 subjects were randomized, 35 to donepezil hydrochloride 3 mg/day, 33 to donepezil hydrochloride 5 mg/day, 37 to donepezil hydrochloride 10 mg/day and 35 to placebo. In the 5 mg group, the initial dose was 3 mg. After 2 weeks, the dose was increased to 5 mg. In the 10 mg group, the initial dose 3 mg. After 2 weeks, the dose was increased to 5 mg. The dose was further increased to 10 mg after dosing at 5 mg for 4 weeks.

Study Outcome Measures

Since this study was an exploratory study, no specific primary endpoint was set and multiplicity test was not taken into consideration.

The ability of donepezil hydrochloride 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 ability of donepezil hydrochloride to improve cognitive function was assessed using a Mini-Mental State Examination (MMSE). The MMSE is a widely used, brief and reliable test for evaluating the cognitive function of patients with neurocognitive disorder.

Behavioral and neuropsychiatric symptoms were assessed using a Neuropsychiatric Inventory (NPI; modified NPI-12). This consisted of 12 items: the original 10 items (delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity; NPI-10), sleep, and cognitive fluctuation, which was reported as Cognitive Fluctuation Inventory. An NPI-2 is a 2-item subscore calculated as the sum of scores for hallucinations and cognitive fluctuation, which correspond to two of the core features of DLB.

Effects on the CIBIC-Plus

The improvement in CIBIC-Plus at the final evaluation (LOCF) was distributed to the improving direction (Table 5), showing a significant difference from placebo group in all donepezil groups (P < 0.001 in the 3 mg group, P = 0.001 in the 5 mg group, P = 0.001 in the 10 mg group; 2-sample Wilcoxon test).

Table 5 - Frequency Distribution of CIBIC-Plus Scores at Week 12 of Treatment of Dementia with Lewy Bodies with Donepezil Hydrochloride: PPS, LOCF

Treatment Group		Markedly Improved	Moderately Improved	Minimally Improved	No change	Minimally Worse	Moderately Worse	Markedly Worse	Total
10 mg	n	1	3	13	8	1	0	0	26
	(%)	(4)	(12)	(50)	(31)	(4)	(0)	(0)	
5 mg	n	5	5	10	4	2	2	0	28
	(%)	(18)	(18)	(36)	(14)	(7)	(7)	(0)	
3 mg	n	1	5	14	6	1	0	1	28
	(%)	(4)	(18)	(50)	(21)	(4)	(0)	(4)	
Placebo	n	0	1	8	5	10	3	0	27
	(%)	(0)	(4)	(30)	(19)	(37)	(11)	(0)	

Effects on the MMSE

The mean differences of MMSE score between donepezil groups and placebo group for the change from Baseline to Week 12 (LOCF) were: 3 mg 1.8 units, 5 mg 4.1 units and 10 mg 2.8 units (Table 6), indicating statistically significant treatment benefits in favor of all donepezil groups over the placebo group (P = 0.046 in the 3 mg group, P < 0.001 in the 5 mg group, P< 0.001 in the 10 mg group; 2-sample *t* test).

Table 6 - MMSE score at Week 12 of Treatment of Dementia with Lewy Bodies with Donepezil Hydrochloride: PPS, LOCF

Treatment Group	Change from Baseline	Treatment Comparisons
	Mean ± S.D.(n)	Mean Difference
10 mg	2.3 ± 3.2 (30)	2.8
5mg	3.5 ± 3.2 (30)	4.1
3 mg	1.2 ± 3.8 (30)	1.8
Placebo	-0.6 ± 2.7 (28)	-

Effects on the NPI-2

The mean differences of NPI-2 score between the donepezil groups and placebo group for the change from Baseline to Week 12 (LOCF) were: 3 mg -2.4 units, 5 mg -3.6 units and 10 mg -5.2 units (Table 7), indicating statistically significant treatment benefits in favor of 5 mg and 10 mg groups over placebo group (P = 0.001 in the 5 mg group, P < 0.001 in the 10 mg group; 2-sample *t* test).

Table 7 - NPI-2 score at Week 12 (LOCF) of Treatment of Dementia with Lewy Bodies with Donepezil Hydrochloride: PPS, LOCF

Treatment Group	Change from Baseline	Treatment Comparisons
	Mean ± S.D.(n)	Mean Difference

10 mg	-5.1±4.6 (31)	-5.2
5 mg	-3.4±3.9 (30)	-3.6
3 mg	-2.2±6.1 (30)	-2.4
Placebo	0.2±4.0 (28)	-

Japanese Confirmatory 12-Week Study

A total of 142 subjects were randomized, 47 to donepezil hydrochloride 5 mg/day, 49 to donepezil hydrochloride 10 mg/day and 46 to placebo. In the 5 mg group, the initial dose was 3 mg. After 2 weeks, the dose was increased to 5 mg. In the 10 mg group, the initial dose 3 mg. After 2 weeks, the dose was increased to 5 mg. The dose was further increased 10 mg after dosing at 5 mg for 4 weeks.

Study Outcome Measures

The effectiveness of treatment with donepezil hydrochloride was determined using a dual outcome assessment strategy that evaluated cognitive function measured by the MMSE and psychiatric symptom and behavioral disorders measured by the NPI-2. The co-primary efficacy variables, using the LOCF imputation for missing data, were used to determine whether each treatment with donepezil 5 mg and donepezil 10 mg has superior efficacy compared to placebo.

The statistical significance both in MMSE and NPI-2 between the placebo group and each donepezil group could determine a superiority of the donepezil over placebo. However, no superiority was demonstrated in either the 5 mg or 10 mg group in the primary analysis.

Effects on the MMSE

The mean differences of MMSE score between each donepezil group and the placebo group for the change from Baseline to Week 12 were: 5 mg 0.8 units and 10 mg 1.6 units (Table 8), indicating a statistically significant treatment benefit in favor of the donepezil 10 mg group over the placebo group (P = 0.016; ANCOVA).

Table 8 - MMSE score at Week 12 (LOCF) of Treatment of Dementia with Lewy Bodies with Donepezil Hydrochloride: FAS, LOCF

Treatment Group	Change from Baseline	Treatment Comparisons
	Mean ± S.E.(n)	Mean Difference
10 mg	2.2±0.4 (49)	1.6
5 mg	1.4±0.5 (43)	0.8
Placebo	0.6±0.5 (44)	-

Effects on the NPI-2

For the mean differences of NPI-2 score at Week 12 (Table 9), there was no significant difference between each treatment of donepezil and placebo.

Table 9 NPI-2 score at Week 12 (LOCF) of Treatment of Dementia with Lewy Bodies with Donepezil Hydrochloride: FAS, LOCF

Treatment Group	Change from Baseline	Treatment Comparisons
	Mean ± S.E.(n)	Mean Difference

10 mg	-2.8±0.5 (49)	-0.7
5 mg	-1.8±0.6 (45)	0.4
Placebo	-2.1±0.6 (44)	-

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-desmethyl donepezil 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 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 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 ^{14}C-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 glucuronide 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 or vascular dementia patients. However mean plasma levels in patients closely agreed with those of young healthy volunteers.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean C_{max} by 39% (see section 4.2).

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*.
There was no evidence of oncogenic potential in long term carcinogenicity studies in either rats or mice.

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, corn starch, hydroxypropyl cellulose, and magnesium stearate.
The film coating contains hydroxypropylmethyl cellulose, talc, polyethylene glycol and titanium dioxide.
Additionally, the 10 mg tablet contains iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container 5 mg tablets:, 10 mg tablets:
Unit dose blister strips (PVC/Aluminium)

6.6 Instruction for use/handling

No special instructions.

7. MANUFACTURER

Eisai Pharmaceuticals India Pvt. Ltd.
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8. IMPORTER

Eisai (Thailand) Marketing Co., Ltd.
Bangkok, Thailand

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

[Date of approval]