Donecept-5 (Donepezil Hydrochloride Tablets 5mg)
Donecept-10 (Donepezil Hydrochloride Tablets 10mg)

Donepezil Hydrochloride

COMPOSITION

Donecept-5

Each tablet contains Donepezil Hydrochloride 5mg.

Donecept-10

Each tablet contains Donepezil Hydrochloride 10mg.

DOSAGE FORM

Film coated tablet

Donecept-5

White, circular, biconvex film coated tablet with '5' debossed on one side and 'DPZ' debossed on the other side.

Donecept-10

Yellow, circular, biconvex film coated tablet with '10' debossed on one side and 'DPZ' debossed on the other side.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase. ATC code: N06DA02

Donepezil hydrochloride is a specific and reversible inhibitor of acetyl cholinesterase, 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 that is present mainly outside the central nervous system.

Alzheimer's Dementia

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 cannot be considered to have any effect on the progress of the disease.

Pharmacokinetics

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-Odesmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. 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-Odesmethyl donepezil (11% - only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-Odesmethyl 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.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean Cmax by 39%.

INDICATIONS

Donecept tablets are indicated for the treatment of mild, moderate and severe dementia in Alzheimer's disease.

DOSAGE AND METHOD OF ADMINISTRATION

Adults/Elderly

Mild to Moderate Alzheimer's Disease

Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil 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 donepezil 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.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil is seen.

Severe Alzheimer's Disease

Donepezil has been shown to be effective at a dose of 10mg administered once daily.

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.

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

Donecept is not recommended for use in children.

Method of Administration

Donecept should be taken orally, in the evening, just prior to retiring.

In case of sleep disturbances including abnormal dreams, nightmares or insomnia, intake of Donecept in the morning may be considered.

CONTRAINDICATIONS

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

WARNING AND PRECAUTIONS

The use of donepezil 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

Donepezil, 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 QT interval prolongation and Torsade de Pointes. Caution is advised in patients with pre-existing or family history of QT prolongation, in patients treated with drugs affecting the QT 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.

Genitourinary

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

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 donepezil 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.

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.

DRUG INTERACTIONS
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 hydrochloride is not affected by concurrent administration of digoxin or cimetidine.

The cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. 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. Ketoconazole reportedly 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 QT 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 QT 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)

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of donepezil in pregnant women. The potential risk for humans is unknown. Donepezil should not be used during pregnancy unless clearly necessary.

Lactation

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Donepzil has minor or 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.

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 as listed below, by system organ class and by frequency.

System organ class	Very common	Common	Uncommon	Rare	Very Rare	Unknown
Infections and infestations		Common cold				
Metabolism and nutrition disorders		Anorexia				
Psychiartic 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	Vomitting Abnormal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers Salivary hypersecretion			
Hepato-biliary disorders				Liver dysfuction including hepatitis***		
Skin and subcutaneous tissue disorders		Rash Pruritis				
Musculoskeletal and connective tissue disorders		Muscle cramps				
Renal and urinary disorders		Urinary incontinence				
General disorders	Headache	Fatigue				

and administration site conditions		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 warnings and precautions).
**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 donepezil should be considered.

OVERDOSE

Dose-related signs of cholinergic stimulation include 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 donepezil 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 coadministered 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).

INCOMPATIBITLITY

Not applicable

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C.

SHELF LIFE
24 months

PACKAGING INFORMATION
One carton containing 3 Alu/PVC/PE/PVDC blisters of 10 tablets.

PRODUCT REGISTRATION HOLDER
Cipla Malaysia Sdn Bhd
Suite 1101, Amcorp Tower,
Amcorp Trade Centre,
18 Persiaran Barat,
46050 Petaling Jaya,
Selangor, Malaysia

MANUFACTURED BY
Cipla Limited,
Plot no. L-139 to L-146,
Verna Industrial Estate,
Verna, Goa, India

DATE OF REVISION
February 2023