MedChoice™ CNS

℞

Donepezil Hydrochloride

Donepedin®

5 mg • **10** mg Film-Coated Tablet

ACETYLCHOLINESTERASE INHIBITOR

FORMULATION
Each film-coated tablet contains:
Donepezil hydrochloride …….. 5 mg, 10 mg

PRODUCT DESCRIPTION
Donepezil Hydrochloride (Donepedin®) 5 mg is a white, round, film-coated tablets engraved with "WI"on one side and "D5" on the other side.
Donepezil Hydrochloride (Donepedin®) 10 mg is a yellow, round, film-coated tablets engraved with "WII"on one side and "D10" on the other side.

INDICATIONS
Symptomatic treatment of mild to moderately severe Alzheimer's dementia.
Treatment of vascular dementia (dementia associated with cerebrovascular disease).

DOSAGE AND ADMINISTRATION
Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). This drug should be taken orally, in the evening, just prior to retiring.
Therefore, because donepezil hydrochloride steady state is achieved about 15 days after it is started and because the incidence of untoward effects may be influenced by the rate of dose escalation, a dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Following a clinical assessment of treatment at 5 mg/day, the dose of this drug 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.
Low-body-weight elderly women, 85 years of age
Close monitoring is required because adverse reactions commonly occur. The maximum daily dose should not exceed 5 mg in low-body-weight elderly women, especially those 85 years of age, due to the potential for significant weight loss
Children:
Experience for pediatric use is limited.

CLINICAL PHARMACOLOGY
Mechanism of Action
Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission.
Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.

PHARMACOKINETICS
Pharmacokinetics of donepezil are linear over a dose range of 1 – 10 mg given once daily. The rate and extent of absorption of Donepezil Hydrochloride (Donepedin) tablets are not influenced by food.
The elimination half-life of donepezil 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 accumulates in plasma by 4-7 fold, and steady state is reached within 15 days. The steady state volume of distribution is 12-16 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha1 – acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.
Donepezil 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 is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation.

PHARMACODYNAMICS
The pharmacotherapeutic group: anti-dementia drugs; anticholinesterase; 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 that is present mainly outside the central nervous system.

SPECIAL WARNING AND PRECAUTIONS FOR USE
1) 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.

① 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, heart block (sinoatrial block or atrioventricular block) or QT prolongation. In particular, patients with cardiac disorders (myocardial infarction, valvular disorder, cardiomyopathy, sick sinus syndrome, abnormal ventricular ECG or intra-atrial or atrioventricular junctional conduction disturbances) and/or with electrolyte abnormalities (hypokalemia, etc.), should be carefully observed to prevent serious arrhythmia from developing. Syncope and seizure have been reported in association with the use of donepezil hydrochloride.

② Gastrointestinal Conditions: 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 nonsteroidal anti-inflammatory drugs (NSAIDS).

③ Neurological Conditions: As stimulating cholinergic nerve of Corpus striatum by cholinomimetic actions, cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms (Parkinson's disease or parkinsonian syndrome), or to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease.

④ Respiratory Conditions: Because of increasing contraction of bronchial smooth muscle or bronchial secretion by cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

2) Donepezil 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

3) Anesthesia: This drug, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

GENERAL CAUTION
1) Patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block (Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., arrhythmia, bradycardia).
2) 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.
3) Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.
4) Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms (Parkinson's disease, Parkinsonian syndrome)

CONTRAINDICATIONS
1) Patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.
2) Pregnant woman or nursing mothers.

ADVERSE REACTIONS

Mild to Moderate Alzheimer's Disease
(1) Followings are the major adverse reactions with unclear frequency that were reported in clinical trial, considered as causal relationship with this drug. In the event of the following symptoms, appropriate measures including drug discontinuation should be taken.
① Syncope, bradycardia, heart block, prolonged QT interval, myocardial infarction, cardiac failure
② Peptic ulcer, perforating duodenal ulcer, GI bleeding
③ Hepatitis, hepatic dysfunction, jaundice
④ Cerebral seizure (epilepsy, convulsion), cerebral bleeding, cerebrovascular disease
⑤ Extrapyramidal disorder: Dysergia, ataxia, motor abnormality, dystonia, tremor, involuntary movement, gait disturbance, abnormal position, extrapyramidal disorder such as language disorder
⑥ Malignant syndrome: Symptoms such as akinetic mutism, extreme muscular rigidity, dysphagia, tachycardia, change in blood pressure and sweating may occur. Such symptoms accompany high fever. In this case, drug discontinuation is exercised and intensive therapy such as systemic therapy for decreasing fever, supplying body fluid or electrolyte should be conducted. Because increase in WBC and CK (CPK) may cause renal function disorder accompanying myoglobulinuria, careful observation is necessary.
⑦ Because rhabdomyolysis may occur, muscle pain, weakness, CK (CPK) elevation in blood and urine should be carefully monitored. Cautions should be exercised for renal function disorder due to rhabdomyolysis.
⑧ Dyspnea
⑨ Acute pancreatitis
⑩ Acute renal failure
⑪ Unknown death

(2) Adverse reactions with or without causal relationship with this drug
① Blood or Lymphonodus : ecchymosis
② Nervous : Abnormal dream

(3) Most Frequent Adverse Events Seen in Association with the Use of this drug
The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving this drug and at twice or more the placebo rate, are largely predicted by this drug's cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and ecchymosis. These adverse events were often of mild intensity and transient, resolving during continued donepezil hydrochloride treatment without the need for dose modification.

DRUG INTERACTIONS
1) In vitro studies have shown that the CYP P450 and to a minor extent CYP 2D6 are involved in the metabolism of donepezil. It is not known the degree of inhibition or induction but caution is exercised in the concurrent use with the following drugs.
① CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as quinidine and fluoxetine could inhibit the metabolism of donepezil.
② CYP3A4 Enzyme inducers, such as rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital and alcohol may reduce the levels of donepezil and drug effect.
2) There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents.
3) Because the concurrent use with cholinergic drugs (capronium, betanechol, aclatonium napadisilate) or acetylcholine esterase inhibitor (ambenonium, distigmine, pyridostigmine, neostigmine) may enhance cholinergic action, it should be avoided.
4) In concomitant use of this drug with anticholinergic drugs (atropine, scopolamine, trihexyphenidyl, pyroheptine, biperiden), antagonic action may reduce drug effect.
5) 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
6) There is also the potential for synergistic activity in the concomitant treatment with beta blocking agents which have effects on cardiac conduction.
7) In the concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), cholinergic action may increase gastric secretion to cause ulcer.

PREGNANCY AND LACTATION
1) 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 peri- and post-natal toxicity. The potential risk for humans is unknown.
2) 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.

PEDIATRIC USE
Safety for pediatric use has not been established. (No experience for pediatric use).

OVERDOSAGE AND TREATMENT
1) Symptoms : Over dosage 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.

2) Treatment : As in any case of overdose, general supportive measures should be utilized. Tertiary anticholinergics such as atropine may be used as an antidote for this drug 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).

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction."

CAUTION ON STORAGE
1) Keep out of reach of children.
2) Changing container may cause misuse and is not recommended in aspect of quality maintenance.
3) Since this drug may be discolored by light, it should be preserved in PTP package.

STORAGE
Store at temperatures not exceeding 30˚C.

AVAILABILITY
Donepezil Hydrochloride (Donepedin®) 5 mg and 10 mg Film-Coated Tablet: Alu/PVC/PVDC blister pack x 10's (Box of 30's).

REGISTRATION NUMBER
Donepezil Hydrochloride (Donepedin®) 5 mg Film-Coated tablet- DRP-8757-01
Donepezil Hydrochloride (Donepedin®) 10 mg Film-Coated tablet- DRP-8758-01

DATE OF FIRST AUTHORIZATION
Donepezil Hydrochloride (Donepedin®) 5 mg Film-Coated tablet- August 06, 2021
Donepezil Hydrochloride (Donepedin®) 10 mg Film-Coated tablet- August 06, 2021

DATE OF REVISION OF PACKAGE INSERT: September 2021

Manufactured by:
Whan In Pharm. Co., Ltd.
50, Gongdan-ro, Anseong-si, Gyeonggi-do
Republic of Korea

Imported by:
JLT Pharma, Inc.
17th Lounge, Medical Plaza
Ortigas Bldg., San Miguel Ave., Ortigas Center,
San Antonio, District 1, Pasig, Metro Manila

Distributed by:
MEDCHOICE CNS PHARMA CORPORATION
10F Unit 1001, 88 Corporate Center, Sedeño cor.
Valero Sts., Salcedo Village, Makati, Metro Manila

3018313-0