DONEPEZIL HYDROCHLORIDE

DOPEZIL®

5 mg & 10 mg FILM-COATED TABLET

CHOLINESTERASE INHIBITOR

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

PHARMACOLOGIC CATEGORY
Cholinesterase Inhibitor

PRODUCT DESCRIPTION
Donepezil hydrochloride 5 mg Tablet: white to off-white, round, film-coated tablet, debossed with "J" on one side and "5" on the other.
Donepezil hydrochloride 10 mg Tablet: white to off-white, round, film-coated tablet, debossed with "J" on one side and "10" on the other.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Alzheimer's disease has been shown to be associated with a relative decrease in cholinergic system activity in the cerebral cortex and other areas of the brain.

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase (AChE), the predominant cholinesterase in the brain. It exerts its therapeutic effect by enhancing cholinergic function in the central nervous system by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by AChE.

In vitro studies show that the inhibitory activity of donepezil was over 1000 times more potent over AChE than that of butylcholinesterase, an enzyme which is present mainly outside the central nervous system.

There is no evidence that donepezil alters the course of the underlying dementing process.

PHARMACOKINETICS
Donepezil hydrochloride is well absorbed with a relative oral bioavailability of 100%. It reaches peak plasma concentrations in 3-4 hours. Oral administration of donepezil produces highly predictable plasma concentrations; plasma concentrations and area under the curve (AUC) rise in proportion to the dose. Neither food nor time of administration (morning vs evening dose) influences the rate or extent of donepezil hydrochloride absorption.

Following multiple dose administration, donepezil 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.

A randomized, open-label, single-dose, two-way cross-over study, involving 28 healthy adult subjects (18-55 years old), was done to compare the bioavailability, characterize the pharmacokinetic profile and assess bioequivalence of the test formulation, Dopezil 5 mg tablet, and 5 mg tablet of a reference standard. The results showed that 90% CI for maximum plasma concentration (C_{max}), AUC_{0-t} and AUC_{0-inf} are within the predefined bioequivalence limits of 80 to 125%.

Donepezil's steady state volume of distribution is 12 L/kg. It 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 2-1,000 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 have been identified. Donepezil is metabolized by the CYP450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The rate of metabolism of donepezil is slow and does not appear to be saturable.

After administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. 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 dose recovered in the urine as unchanged drug. Evidence on enterohepatic recirculation of donepezil and/or any of its metabolites has not been established.

The elimination half-life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Plasma donepezil concentrations decline with a half-life of approximately 70 hours.

Special Populations:
Renal Impairment
A study of patients with moderate to severe renal impairment (Cl < 18 mL/min/1.73 m^2) showed that donepezil clearance did not differ from age- and sex-matched healthy subjects.

Hepatic Impairment
A study of patients with stable alcoholic cirrhosis showed that donepezil clearance was decreased by 20% relative to healthy age- and sex-matched subjects.

Elderly
Donepezil's mean plasma concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's disease are comparable to those observed in young healthy volunteers.

INDICATIONS
- For the treatment of mild, moderate and severe Alzheimer's disease
- For the treatment of vascular dementia (dementia associated with cerebrovascular disease)

DOSAGE AND ADMINISTRATION
General Dosing Recommendation:
Donepezil hydrochloride is administered once daily with or without food. It should be taken in the evening, just prior to retiring.

Individual response to donepezil can not be predicted. Treatment should be continued for as long as a therapeutic benefit for the patient exists.

Recommended Oral Donepezil Dose in Adults/Elderly:

Initial treatment: 5 mg once a day;
The 5 mg once a 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 to be achieved.

Following a one-month clinical evaluation of treatment at 5 mg once a day, the dose of donepezil can be increased to 10 mg once a day.

Maximum recommended dose: 10 mg once a day;
Doses greater than 10 mg once a day have not been studied in clinical trials.

Discontinuation of treatment:
Discontinuation of therapy should be considered where there is no longer evidence of a therapeutic effect, which should be assessed by periodic evaluations by the physician using input from the patient and caregiver.

Upon discontinuation of treatment, a gradual decrease of the therapeutic effects of donepezil is observed.
There is no evidence of a rebound effect after abrupt discontinuation of therapy.

Titration
Studies in patients with mild to moderate Alzheimer's disease showed that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events compared to the 5 mg dose.

Since donepezil 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 given until patients have been on a daily dose of 5 mg for 4-6 weeks.

For patients with renal or mild to moderate hepatic impairment:
A similar dosing schedule can be followed for patients with renal or mild to moderate hepatic impairment since clearance of donepezil is not significantly affected by these conditions.

Or, as prescribed by a physician.

CONTRAINDICATION
- Hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any ingredient in the product.

WARNINGS AND PRECAUTIONS
Cardiovascular conditions
Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes because of their pharmacological action. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Cases of syncopal episodes in association with the use of donepezil have also been reported.

Gastrointestinal conditions
Cholinesterase inhibitors may be expected to increase gastric acid secretion, through their primary action, due to increased cholinergic activity. Thus, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, particularly those at increased risk for developing ulcers (e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs including high doses of acetylsalicylic acid).

However, clinical studies with donepezil have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil hydrochloride 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. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil. Treatment with the 5 mg/day dose for 4 to 6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance.

Neurological conditions
Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease.

There have been very rare post-marketing reports of neuroleptic malignant syndrome (NMS) in patients treated with donepezil 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, donepezil therapy should be discontinued.

Mortality in subjects with vascular dementia
Three clinical trials of six months duration were conducted involving individuals meeting the National Institute of Neurological Disorders and Stroke (NINDS)-Association International pour la Recherche et l'Enseignement en Neurosciences (AIREN) for probable or possible vascular dementia (VaD) and excluding patients with a diagnosis of Alzheimer's disease. The mortality rate for the three VaD studied combined in the donepezil 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 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 group relative to placebo.

When Alzheimer's disease studies were pooled, the mortality rate in the placebo group numerically exceeded that in the donepezil group. There is no evidence of an increased risk of mortality in the current approved indication of mild to moderately severe Alzheimer's disease.

Aggressive behavior
In patients with severe Alzheimer's disease, donepezil should be used with caution in patients with risk of aggression.

Rhabdomyolysis
Rare cases of rhabdomyolysis (including acute renal failure) have been reported in patients treated with donepezil, particularly in the days following dose initiation and dose increase. Majority of these cases occurred independently of the occurrence of 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 levels should be assessed in patients experiencing these symptoms. Donepezil 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 donepezil should be made based on the clinical judgment of the treating physician, in most postmarketing cases, therapy was withdrawn when CPK levels were 5X upper limit of normal or higher. Caution should be particularly exercised in prescribing donepezil 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).

Genitourinary
Although not observed in clinical trials, cholinomimetics may cause bladder outflow obstruction.

Pulmonary conditions
Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease because of their cholinomimetic actions.

Anesthesia
Donepezil hydrochloride may exaggerate succinylcholine-type muscle relaxation during anesthesia.

Hepatic conditions
There is limited information regarding the pharmacokinetics of donepezil in hepatically impaired Alzheimer disease patients. Therefore, close monitoring for adverse effects in patients with hepatic disease being treated with donepezil is recommended.

Renal conditions
There is limited information regarding the pharmacokinetics of donepezil in renally impaired Alzheimer disease patients. Therefore, close monitoring for adverse effects in patients with renal disease being treated with donepezil is recommended.

Effects on Ability to Drive and Use Machine
Alzheimer's dementia may cause impairment of driving performance or compromise the ability to use machinery. In addition, donepezil can cause 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 machinery.

Interactions with Other Medicaments
Effects of other drugs on the metabolism of donepezil: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil.

Inducers of CYP2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care.

Pharmacokinetic studies showed that the metabolism of donepezil is not significantly affected by concurrent administration of digoxin or cimetidine.

Effect of donepezil on the metabolism of other drugs: *In vitro* studies show a low rate of donepezil binding to CYP3A4 and CYP2D6 isoenzymes, which, given the therapeutic plasma concentrations of donepezil, indicates the little likelihood of interferences.

The administration of donepezil had no clinically significant effect on the pharmacokinetics of ketoconazole.

It is not known whether donepezil has any potential for enzyme induction.

Formal pharmacokinetic studies evaluated the potential of donepezil for interaction with theophylline, cimetidine, warfarin, and digoxin. No significant effects on the pharmacokinetics of these drugs were observed.

Anticholinergics: Cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications because of their mechanism of action.

Cholinomimetics and other cholinesterase inhibitors (e.g., succinylcholine, bethanecol): A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonist such as bethanechol.

Drugs highly bound to plasma proteins (e.g., furosemide, digoxin, warfarin): Donepezil did not affect the binding of furosemide, digoxin and warfarin to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy
Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. Thus, donepezil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
It is not known whether donepezil is excreted in human milk. Caution should be exercised when donepezil is administered to a breastfeeding woman.
Children
There are no adequate and well-controlled trails to document the safety and efficacy of donepezil in any illness occurring in children. Thus, donepezil is not recommended for use in children.

Elderly
In Alzheimer's disease patients, nausea, diarrhea, vomiting, insomnia, fatigue, and anorexia increased with dose and age, and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of donepezil in low body weight elderly patients, particularly in those ≥85 years old.
There is limited safety information for donepezil in patients with mild to moderate or severe Alzheimer's disease and significant comorbidity. The use of donepezil in Alzheimer's disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of donepezil doses above 5 mg in this patient population. In severe Alzheimer's disease, the possibility of comorbid vascular disease and risk factors for vascular adverse events and mortality should be considered.

UNDESIRABLE EFFECTS
Infections and infestations: Abscess, cellulitis, fungal dermatitis, herpes zoster, influenza, pneumonia, sepsis
Blood and lymphatic system disorders: Anemia, ecchymosis, eosinophilia, erythrocytopenia, leukocytosis, thrombocythemia, thrombocytopenia
Immune system disorders: Allergic reactions
Endocrine disorders: Diabetes mellitus, goiter, hirsutism
Metabolism and nutrition disorders: Appetite increased, B_{12} deficiency anemia, dehydration, edema (face, periorbital, peripheral), gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, hyponatremia, hypoproteinemia, iron deficiency anemia
Psychiatric disorders: Abnormal dreams, abnormal crying, aggression, agitation, anxiety, apathy, aphasia, confusional state, delusions, depression, dysarthria, dysphasia, dysphoria, emotional lability, emotional withdrawal, euphoria, gait abnormality, hallucinations, hostility, insomnia, irritability, melancholia, pacing, paranoia, personality disorder, restlessness, somnolence, wandering
Nervous system disorders: Cerebral infarction, cerebral ischemia, cerebrovascular accident, convulsion, dementia, dizziness, extrapyramidal syndrome, headache, hemiplegia, hypertonia, hypoesthesia, hypokinesia, intracranial hemorrhage, nervousness, neuralgia, neurodermatitis, neuroleptic malignant syndrome, paresthesia, salivation increased, somnolence, transient ischemic attack, tremor, vertigo
Eye disorders: Abnormal vision, blepharitis, blurred vision, cataract, conjunctival hemorrhage, conjunctivitis, dry eyes, eye irritation, glaucoma, lacrimation disorder, nystagmus, retinal hemorrhage, spots before eyes
Ear and labyrinth disorders: Earache, ear buzzing, hearing decreased, motion sickness, otitis externa, otitis media, tinnitus
Cardiac disorders: Angina pectoris, arrhythmia, atrial fibrillation, AV block (first degree), bradycardia, cardiomegaly, chest pain, electrocardiogram abnormal, heart failure, myocardial infarction, premature ventricular contraction, supraventricular tachycardia, ventricular extrasystoles
Vascular disorders: Arteritis, deep vein thrombosis, hot flashes, hemorrhage, hypertension, hypotension, peripheral vascular disease, postural hypotension, syncope, vasodilation
Respiratory, thoracic and mediastinal disorders: Asthma, bronchitis, cough, dyspnea, epistaxis, hyperventilation, hypoxia, nasopharyngitis, pharyngitis, pleurisy, postnasal drip, pulmonary collapse, pulmonary congestion, sleep apnea, snoring, sore throat, wheezing
Gastrointestinal disorders: Bad taste, bloating, constipation, cholelithiasis, diarrhea, diverticulitis, drooling, dry mouth, duodenal ulcer, dyspepsia, dysphagia, epigastric distress, epigastric pain, eructation, esophagitis, fecal incontinence, fever sore, flatulence, gastritis, gastrointestinal bleeding, gastroenteritis, gingivitis, hemorrhoids, hiatus hernia, ileus, irritable colon, melena, nausea, periodontal abscess, periodontitis, polydipsia, rectal hemorrhage, stomach ulcer, thirst increased, tongue edema, toothache, vomiting
Hepatobiliary disorders: Alanine transaminase increased, aspartate aminotransferase increased, bilirubinemia, gamma glutamyl transpeptidase increased, jaundice, liver function tests abnormal
Skin and subcutaneous tissue disorders: Abrasion, alopecia, dermatitis, diaphoresis, dry skin, eczema, erythema, hyperkeratosis, night sweats, pruritus, psoriasis, rash, skin discoloration, urticaria, skin striae, skin ulcer, vesiculobullous rash
Musculoskeletal and connective tissue disorders: Arthralgia, arthritis, arthrosis, back pain, bone fracture, hypertonia, leg cramps, muscle cramps, myalgia, muscle weakness, muscle fasciculation, muscle spasm, osteoarthritis, osteoporosis
Renal and urinary disorders: Albuminuria, cystitis, enuresis, frequent urination, dysuria, glycosuria, hematuria, inability to empty bladder, hypertrophy, metrorrhagia, nocturia, pyelonephritis, renal failure, urinary incontinence, urinary urgency, urinary tract infection
Reproductive system and breast disorders: Breast fibroadenosis, breast fibrocystic, libido decreased, libido increased, mastitis, vaginitis
General disorders and administration site conditions: Ataxia, asthenia, cachexia, chills, coldness (localized), fatigue, fever, pain (various locations), generalized coldness, head fullness, head pressure, listlessness, malaise
Investigations: Alkaline phosphatase increased, anorexia, blood creatine phosphokinase increased, blood urea nitrogen increased, creatinine increased, lactate dehydrogenase increased, transaminases increased, weight decrease, weight increased
Injury, poisoning and procedural complications: Accident, assault, contusion, fall, skin laceration

OVERDOSAGE & MANAGEMENT
Overdosage with cholinesterase inhibitors can cause cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Also, there is a possibility of increasing muscle weakness which may result in death if respiratory muscles are involved.
General supportive measures should be utilized. Tertiary anticholinergics (e.g., atropine) may be used as an antidote for donepezil overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1-2 mg IV with subsequent doses based on clinical response.
There have been reports of atypical responses in blood pressure and heart rate with other cholinomimetics when concomitantly given 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).

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Dopezil 5 mg Film-Coated Tablet - Blister Foil Pack of 10's (Box of 30's) DR-XY37545
Dopezil 10 mg Film-Coated Tablet - Blister Foil Pack of 10's (Box of 30's) DR-XY37546

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

Store at temperatures not exceeding 30°C.

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Manufactured by Jubilant Generics Limited
Village Sikandarpur, Bhainswal, Roorkee - Dehradun Highway
Bhagwanpur, Roorkee, District Haridwar
Uttarakhand, India-247661, India
Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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*Reg. IPOPHIL