8055248-6713

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

# TORPEZIL

(Donepezil Hydrochloride Tablets U.S.P., 5mg/10mg)

**COMPOSITION**

**TORPEZIL 5mg**

Each film coated tablet contains:

Donepezil Hydrochloride U.S.P. 5 mg

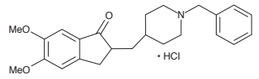
**TORPEZIL 10mg**

Each film coated tablet contains:

Donepezil Hydrochloride U.S.P. 10 mg

**DESCRIPTION**

Donepezil Hydrochloride is white to off white crystalline powder. Freely soluble in chloroform, Soluble in water and in glacial acetic acid. Slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane. Soluble in Methanol & Methylene chloride. Chemically it is 1-benzyl-4-((5,6-dimethoxy-1- indanon)-2-yl) methyl-piperdine hydrochloride. The molecular formula is $C_{24}H_{29}NO_3$*HCl, which corresponds to a molecular weight of 415.96. It has the following structural formula.




Donepezil Hydrochloride

**CLINICAL PHARMACOLOGY**

**Pharmacodynamic:**

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 butyryl cholinesterase, an enzyme which is present mainly outside the central nervous system.

**Pharmacokinetic:**

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.

Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil in 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 14C-labelled 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.

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-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

**INDICATIONS**

Donepezil is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

*Anaesthesia:* Donepezil Hydrochloride, 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.

*Gastrointestinal Conditions:* Patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent no steroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with Donepezil Hydrochloride 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 Donepezil Hydrochloride, cholinomimetics may cause bladder outflow obstruction.

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

Cholinomimetics may have the potential to exacerbate or induce extra pyramidal 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 administeration 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.

**In pregnancy**

Teratology studies conducted in pregnant rats at doses up to approximately 80 times the human dose and in pregnant rabbits at doses up to approximately 50 times the human dose did not disclose any evidence for a teratogenic potential. However, in a study in which pregnant rats were given approximately 50 times the human dose from day 17 of gestation through day 20 postpartum, there was a slight increase in stillbirths and a slight decrease in pup survival through day 4 postpartum. No effect was observed at the next lower dose tested, approximately 15 times the human dose. Donepezil should not be used during pregnancy. For donepezil no clinical data on exposed pregnancies are available.

**In 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 should not breast feed.

**ADVERSE REACTIONS**

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: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

| System Organ Class | Common | Uncommon | Rare |
|---|---|---|---|
| Infections and infestations | Common cold | | |
| Metabolism and nutrition disorders | Anorexia | | |
| Psychiatric disorders | Hallucinations<br>Agitation<br>Aggressive behavior | | |
| Nervous system disorders | Syncope<br>Dizziness<br>Insomnia | Seizure | Extra pyramidal symptoms |
| Cardiac disorders | | Bradycardia | Sino-atrial block<br>Atrioventricular block |
| Gastrointestinal disorders | Diarrhoea<br>Vomiting<br>Nausea<br>Abdominal disturbance | Gastrointestinal haemorrhage<br>Gastric and duodenal ulcers | |
| Hepato-biliary disorders | | | Liver dysfunction including hepatitis |
| Skin and subcutaneous tissue disorders | Rash<br>Pruritis | | |
| Musculoskeletal, connective tissue and bone disorders | Muscle cramps | | |
| Renal and urinary disorders | Urinary incontinence | | |
| General disorders and administration site conditions | Headache<br>Fatigue<br>Pain | | |
| Investigations | | Minor increase in serum concentration of muscle creatine kinase | |

**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.

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.

**DOSAGE AND ADMINISTRATION**

***Adults/Elderly:***

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 in clinical trials.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil 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:***

Donepezil is not recommended for use in children

**OVERDOSAGE**

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 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 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).

**SHELF LIFE**

Do not use later than the date of expiry.

**STORAGE**

Store below 30$^{o}$C.

**PRESENTATION**

TORPEZIL Tablets are available in Alu-Alu blister strip of 10 Tablets.

torrent PHARMA

Manufacture by:

TORRENT PHARMACEUTICALS LTD.

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