xxxxxxxx-5253

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

TORPEZIL TABLETS 5 MG
TORPEZIL TABLETS 10 MG

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

BRAND OR PRODUCT NAME

TORPEZIL TABLETS 5 MG

TORPEZIL TABLETS 10 MG

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

TORPEZIL TABLETS 5 MG

Each film coated tablet contains:

Donepezil Hydrochloride U.S.P. ……..…. 5 mg

Colour: Titanium dioxide

TORPEZIL TABLETS 10 MG

Each film coated tablet contains:

Donepezil Hydrochloride U.S.P. …….. 10 mg

Colours: Yellow Oxide of Iron, Red Oxide of Iron and Titanium Dioxide

PRODUCT DESCRIPTION

TORPEZIL TABLETS 5 MG White to off-white, Circular, biconvex film coated tablets debossed with '5' on one side and break line on other side.

TORPEZIL TABLETS 10 MG

Peach coloured, circular, biconvex, film coated tablets debossed with '10' on one side and break line on other side.

DOSAGE FORM

Film coated tablet

PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamics

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 that is present mainly outside the central nervous system.

Alzheimer's Dementia

Upon administration of single daily doses of 5 mg or 10 mg of donepezil in patients with Alzheimer's Dementia, donepezil reported to produce steady-state inhibition of acetyl cholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively. 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

Donepezil is well absorbed with relative oral bioavailability of 100%. 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 elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil reported to accumulates in plasma by 4-7 folds and steady state is reached within 15 days. The steady state volume of distribution is 12 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.

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-desmethyldonepezil 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. It was reported that following administration of a single 5 mg dose of 14C-labelled 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. There are no reports of donepezil pharmacokinetics in healthy elderly subjects or in Alzheimer's or vascular dementia patients. However mean plasma levels in patients reported closely agreed with those of young healthy volunteers.

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

Special Populations

Hepatic Disease: The clearance of donepezil reportedly decreased by 20% in patients with stable alcoholic cirrhosis relative to healthy age and sex matched subjects.

Renal Disease

In patients with moderate to severe renal impairment (ClCr < 18 mL/min/1.73 m2) the clearance of donepezil did not reported to differ from age and sex matched healthy subjects.

Age

Elderly patients with Alzheimer's disease reported comparable mean plasma donepezil concentrations to those observed in young healthy volunteers.

Gender and Race

Gender and race did not affect the clearance of donepezil.

INDICATION

Torpezil is indicated for the treatment of mild, moderate and severe dementia in Alzheimer's disease.

RECOMMENDED DOSAGE AND MODE OF ADMINISTRATION

Adults/Elderly

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

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.

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

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

Torpezil is not recommended for use in children.

Mode of Administration

Torpezil should be taken orally in the evening, just prior to retiring. Torpezil can be taken with or without food.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Anesthesia

Donepezil Hydrochloride tablet, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

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.

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 hydrochloride tablets concomitantly with other inhibitors of acetyl cholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Severe Hepatic Impairment

There are no data for patients with severe hepatic impairment.

INTERACTIONS WITH OTHER MEDICAMENTS

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% in healthy volunteers. 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).

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

Donepezil hydrochloride tablets should only be used during pregnancy if the potential benefits justify the potential risks to the foetus.

Nursing Mother

It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies on lactating women. Donepezil hydrochloride tablets should only be used by a woman who is breast feeding if the potential benefit outweighs the potential risk to the infant.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Mild to Moderate Alzheimer's Disease

Most adverse events are mild in severity and transient in nature. The most common were diarrhea and muscle cramps.

Other side effects were fatigue, nausea, vomiting, insomnia, and dizziness. There have been reports of psychiatric disturbances, including hallucinations, agitation and aggressive behavior which were resolved on dose reduction or discontinuation of treatment.

No notable abnormalities in laboratory values were observed. Treatment can be associated with minor increases in muscle creatine kinase blood concentrations.

Severe Alzheimer's Disease

The most common adverse events were diarrhea, nausea and aggression.

Vascular Dementia

A comparison of the Alzheimer's disease and Vascular Dementia studies showed that the types of and relative proportions of adverse events associated with donepezil were similar in the two.

Cardiac disorders

Frequency 'not known': polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged.

OVERDOSE AND TREATMENT

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.

Management of Overdose

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 hydrochloride tablets 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).

STORAGE CONDITIONS

Store below 30^{o}C.

PACKAGING AVAILABLE

Donepezil Hydrochloride tablets U.S.P. are packed in Alu-Alu blister of 10 tablets. Such blisters containing 10 tablets are packed into boxes of 10's, 30's and 100's.

"Not all presentations may be available locally"

DATE OF REVISION OF PACKAGE INSERT

28/06/2025

torrent PHARMA

Manufactured by:
TORRENT PHARMACEUTICALS LTD
Indrad - 382 721, Dist. Mehsana, INDIA.

PRODUCT NAME :	Torpezil	**COUNTRY :** Malaysia	**LOCATION :** Indrad		**Supersedes A/W No.:**		
ITEM / PACK :	Insert	**NO. OF COLORS:** 1	**REMARK :**				
DESIGN STYLE :		**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE :	xxxxxxxxx-5253		**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM) (LxWxH) :	180 x 240		Prepared By	**Pkg.Dev**			
ART WORK SIZE :	S/S	Black	Reviewed By	**Pkg.Dev**			
DATE :	14-07-2025		Approved By	**Quality**			