TONIZEP ORALLY DISINTEGRATING TABLET 5MG & 10MG

CONTENT

TONIZEP ODT 5: 5 mg donepezil hydrochloride tablets each containing 4.56 mg donepezil free base.
TONIZEP ODT 10: 10mg donepezil hydrochloride tablets each containing 9.12 mg donepezil free base.

DESCRIPTION

Orodispersilble tablets.
TONIZEP ODT 5: white, round tablet embossed with “5” on one side and “ZD” on another.
TONIZEP ODT 10: yellow, round tablet embossed with “10” on one side and “ZD” on another side.

PHARMACODYNAMICS

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

Alzheimer's Dementia

Administration of single daily doses of 5 mg or 10 mg of donepezil hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetylcholinesterase (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 known. Thus, donepezil hydrochloride cannot be considered to have any effect on the progress of the disease.

An analysis was done at the conclusion of donepezil hydrochloride treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

Those fulfilled the criteria listed below were considered treatment responders.
Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC+
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

	% Response	
	Intent to Treat Population n = 365	Evaluable Population n = 352
Placebo Group	10%	10%
Donepezil HCl 5-mg Group	18%*	18%*
Donepezil HCl 10-mg Group	21%*	22%*

* $p < 0.05$
** $p < 0.01$

Donepezil hydrochloride produced a dose-dependent statistically significant increase in the percentage of those who were judged treatment responders.

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 6-0-desmethyl donepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively known. 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 ^{14}C-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.

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally known in healthy elderly or in those with Alzheimer's or vascular dementia. However, mean plasma levels of donepezil hydrochloride in those with Alzheimer's or vascular dementia closely agreed with the young and healthy.

Those who had mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean C_{max} by 39%.

INDICATION

Tonizep Orally Disintegrating Tablet is indicated for the treatment of mild, moderate, and severe dementia in Alzheimer's Disease.

RECOMMENDED DOSAGE AND MODE OF ADMINISTRATION

Adults/Elderly:

Mild to Moderate Alzheimer's Disease

Treatment is initiated at 5mg/day (once-a-day dosing). Donepezil hydrochloride should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. The 5mg/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 5mg/day, the dose of donepezil hydrochloride can be increased to 10mg/day (once-a-day dosing). The maximum recommended daily dose is 10mg. Doses greater than 10mg/day have not been studied in clinical trials.

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

Severe Alzheimer's Disease

Donepezil hydrochloride has been shown to be effective in controlled clinical trials at a dose of 10mg administered once daily.
Evidence from the controlled trials in mild to moderate Alzheimer's Disease indicates that the 10mg dose, with one-week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5mg and 10mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, a dose of 10mg should not be escalated until patients have been on a daily dose of 5mg for 4 to 6 weeks. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of donepezil hydrochloride is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

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 hydrochloride 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:
Tonizep Orally Disintegrating Tablet is not recommended for use in children.

CONTRAINDICATION
Tonizep Orally Disintegrating Tablet is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

WARNINGS AND PRECAUTIONS
Each tablet contains aspartame. Unsuitable for phenylketonurics.

The use of donepezil hydrochloride in patients with severe dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.

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.

There have been post-marketing reports of QT interval 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 drug 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. 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 of donepezil hydrochloride, 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 hydrochloride 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.

INTERACTION WITH OTHER MEDICAMENTS

Donepezil hydrochloride and/or any of its metabolites does 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 CY P3A4 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 that 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 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)

PREGNANCY AND LACTATION

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.

Tonizep Orally Disintegrating Tablet should not be used during pregnancy unless clearly necessary.

Lactation

Donepezil hydrochloride is excreted in the milk of rat. 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 breastfeed.

SIDE EFFECTS

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations		Common cold				
Metabolism and nutrition disorder		Anorexia				
Psychiatric 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	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers			
Hepato-biliary disorders				Liver dysfunction including hepatitis***		
Skin and subcutaneous tissue disorders		Rash Pruritis				
Musculoskeletal, connective tissue and bone disorders		Muscle cramps			Rhabdomyolysis ****	
Renal and urinary disorders		Urinary incontinence				
General disorders and administration site conditions	Headache	Fatigue Pain				
Investigations			Minor increase in serum concentration of muscle creatine kinase			
Injury and poisoning		Accident				

*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered
**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 hydrochloride should be considered.
**** Rhabdomyolysis has been reported to occur independently of neuroleptic malignant syndrome and in close temporal association with donepezil initiation or dose increase.

Post-Marketing Experience
There have been post-marketing reports of hallucinations, agitation, aggressive behaviour, seizure, hepatitis, gastric ulcer, duodenal ulcer, and gastrointestinal haemorrhage.

SYMPTOMS AND TREATMENTS OF OVERDOSE
Donepezil hydrochloride is a specific reversible acetylcholinesterase inhibitor.

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice and rats in 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 *Tonizep Orally Disintegrating Tablet* 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 (haemodialysis, peritoneal dialysis, or hemofiltration).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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.

STORAGE CONDITION

Tablet may change colour with light, so keep in aluminium pouch until taken.
Store in tight containers at temperature below 30°C.
Keep out of reach of children.
Jauhi daripada kanak-kanak

DOSAGE FORMS AND PACKAGING AVAILABLE

2 x 14 tablets sealed in aluminium sheet pouch and packed in paper carton.

NAME AND ADDRESS OF MANUFACTURER

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