PACKAGE INSERT TEMPLATE FOR DONEPEZIL FILM COATED & ORODISPERSIBLE TABLET

Brand or Product Name
[Product name] Tablet 5mg
[Product name] Tablet 10mg
[Product name] Orodispersible/Orally Disintegrating Tablet 5mg
[Product name] Orodispersible/Orally Disintegrating Tablet 10mg

Name and Strength of Active Substance(s)
Donepezil hydrochloride …mg equivalent to …mg donepezil

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film coated tablets marked '10' on one side

Pharmacodynamics

Donepezil is a piperidine derivative, chemically distinct from other agents in this class. Donepezil demonstrates relatively high selectivity for central nervous system acetylcholinesterase, with minimal peripheral activity. It reversibly and noncompetitively inhibits centrally-active acetylcholinesterase, the enzyme responsible for hydrolysis of acetylcholine. This is expected to result in increased concentrations of acetylcholine that are available for synaptic transmission. Alzheimer's disease is characterized by cholinergic deficiency in the cortex and basal forebrain, which contributes to cognitive deficits. Donepezil does not alter the course of the underlying dementing process.

Pharmacokinetics

Absorption
Donepezil hydrochloride is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 hours after ingestion. Food did not affect the absorption of donepezil hydrochloride

Distribution
It is about 95% bound to human plasma proteins, mainly albumin.

Metabolism
Donepezil is metabolized in the liver. Donepezil undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. About 11% of a dose is present in plasma as 6-O-desmethyldonepezil, which has similar activity to the parent compound.

Excretion
Over 10 days, about 57% of a dose is recovered from the urine as unchanged drug and metabolites, and about 15% from the faeces; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 hours. Steady-state concentrations are achieved within 3 weeks of the start of therapy.

*Sex, race and smoking history have no clinically significant influence or plasma concentrations of donepezil hydrochloride.

Indication
Donepezil tablets are indicated for the treatment of mild, moderate, and severe dementia in Alzheimer's disease.

Recommended Dosage

Adults/Elderly

Mild to Moderate Alzheimer's Disease

Treatment is initiated at 5mg/day (once-a-day dosing). Donepezil should be taken orally, in the evening, just prior to retiring. 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 4 to 6 weeks of clinical assessment in patients who tolerated treatment at 5mg/day, the dose of Donepezil can be increased to 10mg/day (once-a-day dosing). The maximum recommended daily dose is 10mg.

Severe Alzheimer's Disease

Donepezil is effective at a dose of 10mg administered once daily.
However 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 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.

Children
Donepezil is not recommended for use in children.

Mode of Administration
Oral

**The orodispersible tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient's preference.

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

Warnings and Precautions

Anaesthesia: Donepezil 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.

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 showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

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.

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.

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.

Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity.

There is potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists. Concurrent use of donepezil and succinylcholine may result in prolonged neuromuscular blockade.

No adverse effects related to drug interactions were reported when patients were concomitantly administered donepezil and selective serotonin reuptake inhibitors, neuroleptics or (in a small number of cases) anti-Parkinsonian treatment.

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.

Concurrent use of donepezil and oxybutynin may result in decreased efficacy of the cholinesterase inhibitor.

Concurrent use of donepezil and tolterodine may result in decreased efficacy of the cholinesterase inhibitor.

Concurrent use of donepezil and ramelteon may result in increased ramelteon exposure.

Concurrent use of donepezil and bethanechol may result in cholinergic adverse effects (bradyarrhythmia, bronchospasm, hyperhidrosis, diarrhea, vomiting).

Concurrent use of donepezil and quinidine may result in increased donepezil bioavailability.

Concurrent use of donepezil and ketoconazole may result in increased donepezil bioavailability.

Other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil.

There is also the potential for synergistic activity with concomitant treatment involving beta blocking agents which have effects on cardiac conduction.

Statement on Usage During Pregnancy and Lactation

Pregnancy

There is no adequate data on the use of donepezil in pregnant women. The effects, if any, on the developing fetus are unknown. Until more information is available, donepezil should only be used during pregnancy if the maternal condition justifies the potential risk to the fetus.

Lactation
It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Donepezil 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

Cardiovascular: hypertension, rare cases of angina, bradycardia , atrioventricular block, torsades de pointes, sino-atrial block, bradycardia

Endocrine metabolic: weight decreased, anorexia

Gastrointestinal: diarrheoa, loss of appetite, nausea, vomiting, gastrointestinal hemorrhage, abdominal pain, dyspepsia, gastric and duodenal ulcers

Hematologic: contusion, ecchymosis

Skin: rash, pruritus,

Hepatic: Increased liver transaminases, liver dysfunction including hepatitis

Musculoskeletal: muscle cramps, increased creatine kinase level

Neurologic: asthenia, dizziness, headache, insomnia, somnolence, seizures, syncope, extrapyramidal symptoms

Psychiatric: depression, dream disorder, hallucinations, agitation, aggressive behaviour, confusion

Renal and urinary disorders: urinary incontinence, urinary-tract infections

Other: fatigue, upper-respiratory-tract infections, sweating

Overdose and Treatment

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.
Treatment is symptomatic and supportive. 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 anti- cholinergics 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
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]