



# A strategic move



## Donecept

Donepezil 5mg and 10mg film-coated tablets  
Anticholinesterase

**Composition:** Each tablet contains 5mg or 10mg donepezil hydrochloride. **Therapeutic indications:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Posology and method of administration:** Treatment is initiated at 5 mg/day (once-a-day dosing). Donecept 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 Donecept 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. 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 medicinal product 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. (For doses not realisable/practicable with this strength other strengths of this medicinal product are available.) **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 and adolescents:** Donecept is not recommended for use in children and adolescents. **Contraindications:** Hypersensitivity to the active substance donepezil hydrochloride, piperidine derivatives or to any of the excipients. **Pregnancy. Special warnings and precautions for use:** The use of donepezil in patients with severe Alzheimer's dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated. **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 sino-atrial 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 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:** Although not observed in clinical trials of donepezil, 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 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. **Lactose intolerance:** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Mortality in Vascular Dementia Clinical Trials:** Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride 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 hydrochloride 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 hydrochloride group relative to placebo. In pooled Alzheimer's disease studies (n = 4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n = 6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups. **Interaction with other medicinal products and other forms of interaction:** 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, 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. **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 postnatal toxicity. The potential risk for humans is unknown. Donecept must not be used during pregnancy. **Lactation:** Donepezil is excreted in the milk of rats. 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. **Effects on ability to drive and use machines:** Donecept 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. **Undesirable effects:** 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: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) and rare ( $\geq 1/10,000$  to  $< 1/1,000$ ). Very common: diarrhoea, nausea, headache; Common: common cold, anorexia, hallucinations\*\* agitation\*\*, aggressive behaviour\*\*, syncope\*, dizziness, insomnia, vomiting, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, fatigue, pain, accident; Uncommon: seizure\*, bradycardia, gastrointestinal haemorrhage, gastric and duodenal ulcers, minor increase in serum concentration of muscle creatine kinase; Rare: extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis\*\*\* (\*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered. \*\*Reports of hallucinations, agitation and aggressive behaviour have resolved on dose-reduction or discontinuation of treatment. \*\*\*In cases of unexplained liver dysfunction, withdrawal of Donecept should be considered)

**Marketing Authorisation Holder:** Actavis Group PTC ehf, Reykjavikurvegur 76-78, 220 Hafnarfjörður, Iceland. **Supply classification:** This medicinal product is subject to a medical prescription.