ALZIL (Donepezil)

Available as tablets: 5 mg, 10 mg

(1) Indications (for elderly): symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type

(2) Recent trials:

Abstract 1:

Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan.

Homma A, Imai Y, Tago H, Asada T, et al.
Dement Geriatr Cogn Disord. 2009;27(3):232-9. Epub 2009 Feb 25.

BACKGROUND/AIMS: A 6-month, randomized, double-blind, placebo-controlled study was extended to evaluate long-term safety and efficacy of donepezil in community-dwelling Japanese patients with severe Alzheimer's disease (AD).

METHODS: 189 patients were enrolled from the double-blind study into a 52-week, open-label extension study. After a 2- to 8-week washout, donepezil was escalated within 6 weeks to 10 mg/day. Main outcomes were Severe Impairment Battery (SIB), Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for severe AD (ADCS-ADL-sev) and Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Safety parameters were monitored throughout.

RESULTS: Overall, mean change from extension study baseline in SIB scores improved until week 24; however, scores were influenced by prior treatment during the double-blind study and by length of washout. Patients treated with donepezil retained some treatment benefits after a washout of 2-4 weeks but lost all treatment benefits after a washout of 4-8 weeks. There was no change in ADCS-ADL-sev or BEHAVE-AD scores. Adverse events were consistent with the known donepezil safety profile.

CONCLUSION: Donepezil is effective and safe for symptomatic treatment of severe AD for at least 1 year. Patients who receive donepezil 10 mg daily with little or no interruption achieve the best long-term outcome.

Abstract 2:

Treatment of a whole population sample of Alzheimer's disease with donepezil over a 4-year period: lessons learned.

Lyle S, Grizzell M, Willmott S, Benbow S, et al.
Dement Geriatr Cogn Disord. 2008;25(3):226-31. Epub 2008 Jan 30.

BACKGROUND: In the UK it is recommended that acetylcholinesterase inhibitors be restricted to patients with moderate Alzheimer's disease, and progress monitored within specialist clinics. Objective: To describe a cohort of patients with Alzheimer's disease from a whole city population treated with donepezil, and to analyse outcomes over 4 years.

METHODS: Historical cohort design: 88 patients recruited 1997-1998, assessed at baseline with 4-year follow-up, using an agreed protocol and validated measures: survival, retention in treatment, cognition, non-cognitive symptoms, weight change, carer stress.

RESULTS: 64.7% remained on treatment beyond 6 months, 57.9% beyond 1 year and 12.5% beyond 4 years. 56% remained alive at 4 years - almost twice the number predicted. **Mean MMSE score amongst patients in treatment did not deteriorate over 4 years.** Survival, retention in treatment, maintenance/improvement of cognition was greater with high baseline MMSE. Non-cognitive symptoms, carer stress and weight change remained low throughout.

CONCLUSIONS: A minority of people with dementia from the population (88 of potential 2,000 at outset, 11 by 4 years) received treatment. **Benefits for individuals were confirmed, especially for those with mild impairment.** Expenditure on medication was modest in a population context. These findings question recent guidance from the National Institute for Clinical Excellence, which would restrict therapy to patients with moderate cognitive impairment.

Abstract 3:

Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial.

Homma A, Imai Y, Tago H, Asada T, et al.
Dement Geriatr Cogn Disord. 2008;25(5):399-407. Epub 2008 Apr 3

BACKGROUND/AIMS: A 24-week, randomized, parallel-group, double-blind placebo-controlled study was conducted to evaluate the efficacy and tolerability of donepezil in severe Alzheimer's disease (AD).

METHODS: Patients with severe AD (Mini-Mental State Examination score 1-12; modified Hachinski Ischemic Score < or =6; Functional Assessment Staging > or =6) were enrolled in this study in Japan. A total of 325 patients were randomized to donepezil 5 mg/day (n = 110), donepezil 10 mg/day (n = 103) or placebo (n = 112). Primary outcome measures were change from baseline to endpoint in the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus) at the endpoint visit.

RESULTS: Donepezil 5 mg/day and 10 mg/day were significantly superior to placebo on the SIB, with a least-squares mean treatment difference of 6.7 and 9.0, respectively ($p < 0.001$ compared with placebo). CIBIC-plus analyses showed significant differences in favor of donepezil 10 mg/day over placebo at endpoint ($p = 0.003$). A statistically significant dose-response relationship was demonstrated with the SIB and CIBIC-plus. Donepezil was well tolerated.

CONCLUSION: This study confirmed the effectiveness of donepezil 10 mg/day in patients with severe AD and demonstrated a significant dose-response relationship. Donepezil at dosages of both 5 mg/day and 10 mg/day is safe and well tolerated in Japanese patients with severe AD.

Abstract 4:

The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease.

Holmes C, Wilkinson D, Dean C, Vethanayagam S, et al.
Neurology. 2004 Jul 27;63(2):214-9.

OBJECTIVE: To determine the efficacy of donepezil in the treatment of neuropsychiatric symptoms in patients with Alzheimer disease (AD) in a randomized withdrawal study.

METHOD: Patients with mild to moderate AD with marked neuropsychiatric symptoms at baseline (Neuropsychiatric Inventory [NPI] > 11 points) were treated openly with donepezil 5 mg daily for 6 weeks followed by 10 mg daily for a further 6 weeks. Patients were then randomized (60:40) to either placebo or 10 mg donepezil daily. All patients were assessed at 6 weeks and provided there was no marked cognitive deterioration their blinded treatment was continued for a further 6 weeks. NPI and carer distress were assessed at 6 weekly intervals throughout the study.

RESULTS: A total of 134 patients participated. Following randomization patients who continued on donepezil 10 mg for 12 weeks had improvements in NPI compared with the placebo group (mean change -2.9 vs 3.3 points; ITT-LOCF $p = 0.02$) and in NPI-Distress scores (median change -2.0 vs 1.0 points; ITT-LOCF $p = 0.01$). During the open-label phase the total NPI and NPI-Distress scores were lower after 12 weeks treatment with open label donepezil compared with baseline (total NPI 22 points vs13 points; ITT-LOCF $p < 0.0001$; NPI-Distress 13.5 vs 7.9 points; ITT-LOCF $p < 0.0001$). In the open-label

phase all domains of the NPI (with the exception of elation) were improved (all $p < 0.05$ after Bonferroni correction).

CONCLUSIONS: Donepezil has significant efficacy in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD.

(3) Dosage in elderly:

Recommended Dose and Dosage Adjustment

(1) Elderly male and female (< 85 year age) with normal body weight: Start with ALZIL 5 mg once a day. Maintain this for 4-6 weeks and consider dose increase, if required to 10 mg once a day.

(2) Low body weight and elderly females (>85 years): dose should not exceed 5 mg/day.

(3) **Use in Elderly Patients with Comorbid Disease:** Caution is advised regarding the use of **ALZIL** doses above 5 mg in this patient population

Adults: The recommended initial dose of **ALZIL** is 5 mg taken once daily. Therapy with the 5-mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug and to allow plasma levels to reach steady state.

Based on clinical judgment, the 10-mg daily dose may be considered following 4-6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily.

ALZIL should be taken once daily in the morning or evening. It may be taken with or without food.

Special Populations:
Adverse events are more common in individuals of low body weight, in patients ≥85 years old and in females. In elderly women of low body weight, the dose should not exceed 5 mg/day.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

Geriatrics (≥ 65 years of age): In Alzheimer's disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age, and the incidence appeared to be greater in female patients.

Since cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of **ALZIL** in low body weight elderly patients, especially in those ≥ 85 years old.

Use in Elderly Patients with Comorbid Disease: There is limited safety information for **ALZIL** in patients with mild to moderate or severe Alzheimer's disease and significant comorbidity. The use of **ALZIL** in Alzheimer's disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of **ALZIL** doses above 5 mg in this patient population.

(4) Common side effects:

The common side effects include nausea and diarrhea. In clinical studies, these effects were often mild, and generally went away with continued treatment.
Other possible side effects include: insomnia (difficulty sleeping), vomiting, muscle cramps, fatigue, anorexia (loss of appetite) and fainting.