ALZIL M (Donepezil + Memantine)

Available as tablets: Donepezil 5 mg and memantine 5 mg; Donepezil 5 mg and memantine 10 mg

(1) Indications (for elderly): Treatment of patients with moderate to severe dementia o f Alzheimer's type.

(2) Recent trials:

Abstract 1:

Lack of Pharmacokinetic or Pharmacodynamic Interaction between Memantine and Donepezil

Antonia P Periclou, Daniel Ventura, Tyler Sherman, Niranjan Rao, Wattanaporn T Abramowitz.
The Annals of Pharmacotherapy: Vol. 38, No. 9, pp. 1389-1394. Published Online, July 20, 2004

BACKGROUND: Memantine, a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist, was approved in the US for treatment of moderate to severe Alzheimer's disease in October 2003.

OBJECTIVE: To determine whether an in vivo pharmacokinetic interaction exists between memantine and the acetylcholinesterase (AChE) inhibitor donepezil.

METHODS: In this open-label, multiple-dose study, 24 healthy subjects (aged 18–35 y) received oral administration of memantine 10 mg on day 1. Following a 14-day washout period, subjects were orally administered donepezil 5 mg once daily for 7 days on an outpatient basis. Beginning on day 22, the donepezil dosage was doubled for 22 days to the target dose of 10 mg once daily, with the last donepezil dose concomitantly administered with memantine 10 mg on day 43. Assessments included pharmacokinetic as well as safety parameters. In addition, AChE inhibition was measured in red blood cells by radiolabeled-enzyme assay following administration of donepezil alone and after a single memantine dose.

RESULTS: Data from 19 subjects who completed the study indicated no significant pharmacokinetic interactions between a single dose of memantine and multiple doses of donepezil. Percent maximum inhibition of AChE activity (mean ± SD) by donepezil was 77.8 ± 7.3% and not significantly different upon coadministration of a single dose of memantine (81.1 ± 5.7%). Two subjects withdrew due to adverse events while taking donepezil alone. Single memantine doses administered with multiple donepezil doses were well tolerated.

CONCLUSIONS: **The pharmacokinetic and pharmacodynamic data from this study indicated a lack of interaction between memantine and donepezil, suggesting that memantine and donepezil may be safely and effectively used in combination.**

Abstract 2:

Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: an exploratory reanalysis.

Schmitt FA, van Dyck CH, Wichems CH, Olin JT; for the Memantine MEM-MD-02 Study Group.
Alzheimer Dis Assoc Disord. 2006 Oct-Dec;20(4):255-62.

OBJECTIVE: To investigate the cognitive effects of the N-methyl-D-aspartate receptor antagonist, memantine, with a post-hoc exploratory reanalysis of a 24-week randomized, double-blind, placebo-controlled, parallel group clinical trial comparing memantine (20 mg per day) to placebo in patients with moderate to severe Alzheimer disease (AD) receiving treatment with the cholinesterase inhibitor, donepezil.

METHODS: The effects of memantine on individual items of the Severe Impairment Battery (SIB), subscale performance, and 3 post-hoc-derived aggregate subscales were investigated. Analyses were based on the intention-to-treat population using last observation carried forward and observed cases approaches. The SIB components were assessed at baseline, weeks 4, 8, 12, 18, and 24.

RESULTS: The mean change from baseline by visit and at study end point on the SIB showed statistically significant differences between the memantine and placebo groups at all visits beginning at week 8 (last observation carried forward and observed cases). The SIB subscale analysis showed statistically significantly greater effects of memantine than placebo on memory, language, and praxis. When the SIB domains were aggregated using a face valid approach to create 3 higher-order subscales, memantine treatment resulted in statistically significant differences on memory, language, and praxis compared with placebo.

CONCLUSIONS: These post-hoc analyses support the beneficial effects of memantine on cognition observed in a previously reported clinical trial. The results presented here suggest an effect of memantine on memory, language, and praxis in patients with moderate to severe AD and support the efficacy of memantine for the treatment of cognitive deficits in AD.

Abstract 3:

Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy

Hartmann, Susanne; Möbius, Hans Jörg
International Clinical Psychopharmacology:Volume 18(2)March 2003pp 81-85

Memantine, a moderate-affinity, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in dementia, including Alzheimer disease (AD). Therefore, its combination with acetylcholinesterase inhibitors (AChEIs) is anticipated. We report a postmarketing surveillance study conducted among German physicians who, during routine clinical practice, treated demented patients with memantine in combination with an AChEI. Most of the 158 surveyed patients (mean age, 74 years) were diagnosed with AD but other dementias were included. Memantine was prescribed at a wide range of daily doses (median, 20 mg/day) and was combined with donepezil for most patients (84%). Combination therapy was well tolerated for nearly all patients (98%) for an average observation period of 4 months at stable doses of both antidementia agents. No serious adverse drug reaction (ADR) was reported. No ADR or change in blood chemistry was experienced by most patients (96% and 81%, respectively); the six reported ADRs resolved without sequelae and without drug discontinuation. Global clinical status of most patients was judged as improved (54%) or stable (39%) over the observation period. These findings particularly suggest that memantine in combination with AChEIs is safe and well tolerated.

(3) Dosage in elderly:

It depends on the severity of the symptoms and the response of the individual patient. The target dose of Donepezil is 10 mg/day and Memantine 20 mg/day. Dose should be titrated gradually to minimize adverse events [Donepezil titrated at 4-6 weeks and Memantine titrated weekly interval]. So after gradual titration, Donepezil 5 mg + Memantine 10 mg Tablet is to be taken two times a day or as directed by physician. ALZIL M can be taken with or without food.

Use of Donepezil above 5 mg should be with caution in elderly patients with co-morbidity.

Dosage reduction is required in severe renal failure.

(4) Common side effects:

Donpezil:
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.

Memantine:
In general, observed side effects are mild to moderate. The most common side effects are headache, somnolence (excessive sleepiness), constipation and dizziness. Less frequently

tiredness, confusion, vomiting, abnormal gait and hallucinations (mainly seen in patients with severe Alzheimer’s disease) have been reported.