Emerging Drug List
GALANTAMINE

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT

NO. 11 JULY 2001

Generic (Trade Name)**:** Galantamine (Reminyl®)

Manufacturer: Janssen-Ortho Inc. (Toronto, ON)

Indication: For the symptomatic treatment of mild to moderate dementia of the Alzheimer's type.

Current Regulatory Status: The Therapeutic Products Directorate of Health Canada approved Galantamine for the treatment of mild to moderate Alzheimer's disease August 1, 2001. Galantamine was approved by the FDA in February, 2001 and has been available on the U.S. market since early May, 2001.

Description: Galantamine is a selective, reversible, competitive inhibitor of acetylcholinesterase. Clinical trials in Alzheimer's Disease (AD) have used doses of 8, 16, 24 and 32 mg daily given as two divided doses. Galantamine is available in the U.S. as 4, 8 and 12 mg tablets. The recommended starting dose is 8 mg daily in two divided doses for at least four weeks with progression to 16 mg daily thereafter. After an additional four weeks the daily dose may be increased to 24 mg if warranted. Tolerance is improved with slower dose escalation.

Current Existing Treatments: Medications that are currently approved in Canada for symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type include the cholinesterase inhibitors donepezil hydrochloride (Aricept®, Pfizer) and rivastigmine tartrate (Exelon®, Novartis Pharmaceuticals). Metrifonate (ProMem™, Bayer), a third cholinesterase inhibitor, has not been approved for use in Canada.

Cost: The price of the drug in Canada is not yet available..

Evidence: The safety and efficacy of galantamine has been evaluated in large, well designed trials of three to six months in length in patients with mild to moderate AD. The progressive loss of cognitive function, a defining symptom of AD, was the the primary outcome in these studies. Global functioning was also considered in most studies. These parameters were assessed using FDA-approved instruments (e.g. the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC-plus)) in almost all trials. Other instruments, including the Neuropsychiatric Inventory (NPI), the Disability Assessment in Dementia (DAD), the Activities of Daily Living inventory (ADCS-ADL) and the Progressive Deterioration Scale (PDS) were used to measure secondary outcomes.

The FDA recognizes a difference of $ 4 points in ADAS-cog scores when a treatment is compared with placebo as being clinically significant. These differences were generally seen when a dosage regimen of 16 to 32 mg/day of galantamine was used for 3 to 6 months. Global outcomes showed statistically significant differences in favour of treatment when 24 to 36 mg/daily were used for three months duration. A dose of 8 mg per day failed to have a statistically significant effect after six months duration. One trial with 386 patients showed that galantamine (24 to 32mg/day) produced a significant improvement in activities of daily living indicated by a drug-placebo difference in the mean change from baseline DAD scores. The intention-to-treat results were less significant, favouring 32 mg per day of galantamine. No studies as yet have directly compared galantamine to donepezil or rivastigmine.

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Adverse Effects:

Galantamine is generally well tolerated with a safety profile similar to other cholinesterase inhibitors. The most common adverse events occurring with galantamine at doses of 16 or 24 mg/day were tremor, anorexia, vomiting, nausea, weight loss, headache, abdominal pain, diarrhea and dizziness. One study reported agitation occurring significantly more often in patients treated with galantamine (i.e., 15, 10, and 8.1 % with 8, 16, 24 mg galantamine, respectively versus 9.4% with placebo).

Galantamine has the potential to interfere with the activity of anticholinergic medications. A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists like bethanechol. The concurrent administration of cimetidine or ketoconazole, inhibitors of CYP3A4 and CYP2D6 liver enzymes, has significantly increased the AUC of galantamine. Paroxetine, a strong inhibitor of CYP2D6, increased the oral bioavailability of galantamine by approximately 40%.

Conclusion:

Galantamine will be the third anticholinesterase agent to be approved in Canada for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. It will join donepezil (Aricept™) and rivastigmine (Exelon®) as another treatment option. None of these agents alter the underlying, progressive, degenerative process and they are not effective in the majority of patients who are diagnosed with AD. Galantamine at doses greater than 16 mg daily can provide a modest improvement in symptoms with a stabilization of the disease for at least six months. It is anticipated that this response will decrease as the disease progresses. Galantamine compared to placebo had a positive impact on cognitive and global function as well as activities of daily living assessments.

Galantamine, therefore, is another choice for first line treatment of AD, although further studies and a direct comparison of the three agents are needed before recommendations of which agent is preferable can be made.

References:

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