Drug Monograph

Generic Name: Galantamine  
Brand Name: Reminyl®  
Manufacturer: Shire Pharmaceuticals and Janssen Cilag  
(http://www.janssenpharmaceutica.be/index_N.asp)

Summary:
Galantamine hydrobromide, a phenanthrene alkaloid, is a reversible, competitive acetylcholinesterase inhibitor that is structurally unrelated to other acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, tacrine). Galantamine hydrobromide is used for the treatment of mild to moderate dementia of the Alzheimer's type (Alzheimer's disease). Efficacy has been demonstrated in many randomized, placebo-controlled studies of 3-6 months' duration utilizing a dual outcome assessment strategy. The recommended starting dosage of galantamine is 4 mg twice daily. Increases of 8 mg/day, in two divided doses, may be made after at least four weeks at a given dosage. A maintenance dosage of 16-24 mg/day, in two divided doses, has been found to be effective and reasonably tolerated. Comparison of the different reversible inhibitors of acetylcholinesterase used in mild to moderate dementia in Alzheimer’s disease, galantamine has extra mode of action to stimulate nicotinic receptors to release more acetylcholine in the brain.

Pharmacologic Data:
Mechanism of Action
Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine producing neurons degenerate in the brains of patients with Alzheimer’s disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer’s disease). Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase that binds reversibly with and inactivates acetylcholinesterase, thus inhibiting hydrolysis of acetylcholine and increasing the concentration of acetylcholine at cholinergic synapses. The drug also binds allosterically with nicotinic acetylcholine receptors and may potentiate the action of agonists (e.g., acetylcholine) at these receptors. While the precise mechanism of galantamine’s action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. Because a deficiency of acetylcholine caused by selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus is recognized as one of the early pathophysiologic features of Alzheimer's disease associated with memory loss and cognitive deficits, enhancement of cholinergic function with an anticholinesterase agent, such as galantamine, is one of the pharmacologic approaches to treatment. Galantamine's effect may diminish as the disease process advances and fewer cholinergic neurons remain functioning. There is no evidence that galantamine alters the course of the underlying dementing process. [1, 2, 3, 4]

Therapeutic Indications:
Reminyl® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of
Evidence-Based Clinical Guidelines
A search of the literature was performed to identify evidence-based clinical guidelines. This included MEDLINE, EMBASE, National Guideline Clearinghouse web site, the FDA of US, and approximately a dozen internet search engines.

Clinical studies
The efficacy of galantamine has been demonstrated in multiple randomized, Phase III trials of >2,600 patients with mild-to-moderate Alzheimer’s disease (AD) [5]. Studies have found that galantamine improved or maintained performance in all domains of AD (cognition, function, behavior, and caregiver burden) in the short term and slowed the decline in performance or maintained baseline performance through 12 months. Other studies of galantamine demonstrated cognitive, behavioral, and functional benefits in patients with vascular dementia (VaD) and AD with cerebrovascular disease (CVD) [6]. 326 patients with VaD or AD with CVD who completed an initial 12-month trial were treated with galantamine 24 mg/day in a 24-month, open-label extension. Patients taking galantamine for the entire study demonstrated the least cognitive decline on AD Assessment Scale-cog/11: 2.7 points vs. 3.1 points in those given placebo initially (P < 0.001 and P = 0.003, respectively). The long-term benefits of galantamine were evident in both groups; cognitive baseline levels were maintained for approximately 21 months in VaD patients and for 12 months in patients with AD with CVD. In the post hoc analysis of pooled phase III galantamine clinical trials designed to assess whether older (> or =80 years) and younger (< or =79 years) AD patients experience similar benefits with galantamine based on changes in the ADAS-cog and CIBIC-plus [7], mean ADAS-cog scores for older patients treated with galantamine 24 mg/day significantly improved versus baseline and versus placebo at month 3. Cognitive improvement was maintained versus placebo at month 6; the ADAS-cog score for placebo patients dropped below baseline at month 6. Change in CIBIC-plus for galantamine was significantly different from placebo at months 5 to 6. Mean ADAS-cog score in older patients taking galantamine for 12 months remained above baseline. Incidence of adverse events in patients > 80 years was similar to that in the overall study population. Galantamine maintained cognitive and global function in patients > 80 years with mild to moderate AD for at least 5 to 6 months and cognitive efficacy for 12 months. A multicentre, randomized, parallel, double-blind, placebo-controlled trial was carried out to evaluate the efficacy of galantamine 18, 24 and 36 mg/day administered for 3 months in 285 patients with mild-to-moderate probable AD. [8] Patients treated with galantamine 24 mg/day had a significantly better outcome than placebo on ADAS-cog; the treatment difference was 3 points on the intention-to-treat (ITT) analysis (p = 0.01) and 4.2 points on per protocol analysis (p = 0.001). Per protocol analysis showed that galantamine had a significantly better outcome than placebo on PDS (24-mg/day dose, p < 0.05) and CGIC (36-mg/day dose, p < 0.05). In a 6-month, multicenter, double-blind trial was undertaken in 636 patients [9] and a randomized, double blind, parallel group, placebo controlled trial committed in outpatient clinics in Europe and Canada with 653 patients with mild to moderate AD [10], patients were randomly assigned to placebo or galantamine and escalated to maintenance doses of 24 or 32 mg/d. Galantamine significantly improved cognitive function relative to placebo, revealing with ADAS-cog/11 scale at month 6 (p < 0.001). Galantamine produced a better outcome on CIBIC-plus than placebo (p < 0.05). A 5-month multicenter, placebo-controlled, double-blind trial to investigate the efficacy and tolerability of galantamine, using a slow dose escalation schedule of up to 8 weeks, in 978 patients with mild to moderate AD by Tariot et al gave the similar result. [11] Another 5 months study of galantamine also resulted in more improvement in
ADCS/ADL scores (The AD Cooperative Study ADL Inventory) than placebo regardless of baseline dementia severity, with the greatest differences occurring in patients with more severe disease. [12] To conclude, galantamine significantly improves the core symptoms of Alzheimer's disease versus placebo.

For the safety of galantamine, long-term (up to 24 months) galantamine therapy in patients with VaD and AD with CVD is well tolerated and associated with prolonged maintenance of cognitive function. [6] Another study also shows galantamine was well tolerated at the lower doses of 18 and 24 mg/day where it produced mild, transient effects typical of cholinomimetic agents. [8] The most common adverse events, which were predominantly gastrointestinal, decreased in frequency during long-term treatment. [9] Treatment discontinuations due to adverse events in all galantamine groups were (6 to 10%) whereas the discontinuation rate in the placebo group was (7%). [11]

For the comparison of galantamine other drugs in the same class, long-term efficacy and safety of galantamine (n=94) 24 mg/day and donepezil (n=88) 10 mg/day in patients with Alzheimer's disease have been compared. Significant advantages were found in the treatment response to galantamine (versus donepezil) on cognition. [13] However, a clinical trial showed more gastrointestinal side effects were reported for galantamine vs donepezil. [14] From a review article of clinical trials studying patients with mild to moderate Alzheimer’s disease treated with galantamine, donepezil and rivastigmine experienced modest improvements in cognition, function and behaviour. The magnitude of benefits seen with each agent appeared to be similar and the authors concluded that all three agents should be recommended as 1st line drugs in treating mild to moderate Alzheimer’s disease. [15] From meta-analysis, galantamine, donepezil and rivastigmine were found to be superior to placebo, but galantamine and rivastigmine were associated with a greater risk of trial dropout than placebo. [16]

**Bioavailability/Pharmacokinetics**

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.

The maximum inhibition of acetylcholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

**Absorption and Distribution**

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution. Food did not affect the AUC of galantamine but Cmax decreased by 25% and Tmax was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L. The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

**Metabolism and Elimination**

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly.

**Special Populations**

1. **CYP2D6 poor metabolizers**

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a
single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar 
Cmax and about 35% AUC∞ increase of unchanged galantamine compared to extensive metabolizers. 
A total of 356 patients with Alzheimer’s disease enrolled in two phase 3 studies were genotyped with 
respect to CYP2D6 (n=210 heteroextensive metabolizers, 126 homo-extensive metabolizers, and 20 
poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in 
median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not 
necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to 
tolerability.
2. Hepatic Impairment
Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with 
mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In 
patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), galantamine clearance was 
decreased by about 25% compared to normal volunteers. Exposure would be expected to increase 
further with increasing degree of hepatic impairment.
3. Renal Impairment
Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderate and 
severely renal impaired patients compared to normal volunteers
4. Elderly
Data from clinical trials in patients with Alzheimer’s disease indicate that galantamine concentrations 
are 30-40% higher than in healthy young subjects.
5. Gender and Race
No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the 
disposition of Reminyl® (galantamine hydrobromide), but a population pharmacokinetic analysis 
indicates (n= 539 males and 550 females) that galantamine clearance is about 20% lower in females 
than in males (explained by lower body weight in females) and race (n=1029 White, 24 Black, 13 
Asian and 23 other) did not affect the clearance of Reminyl®

Dosage Form
For Oral Use:
- Circular biconvex film-coated tablets:4 mg (off-white), 8 mg (pink), and 12 mg (orange-brown).
- Oral solution 4 mg/mL.

Dosage and Administration
Galantamine hydrobromide is administered orally twice daily, preferably with morning and evening 
meals. Administration of galantamine with food and utilizing a slow, 4-week interval escalation of 
dosages may reduce the incidence of adverse GI effects (e.g., nausea, vomiting).

Dosage of galantamine hydrobromide is expressed in terms of galantamine. The recommended initial 
adult dosage of galantamine is 4 mg twice daily for a minimum of 4 weeks. If this dosage is well 
tolerated, the dosage may be increased to 8 mg twice daily. Subsequent increases to 12 mg twice daily 
should be attempted after a minimum of 4 weeks of treatment at the previous dosage. In clinical studies, 
a dosage of 8-16 mg twice daily was effective; however, the manufacturer recommends a dosage range 
of 8-12 mg twice daily. Use of higher dosages (e.g., 16 mg twice daily) does not result in greater 
efficacy and is less well tolerated than lower dosages. If galantamine therapy has been interrupted for
more than a few days for any reason and re-initiation of the drug is not contraindicated, therapy should be restarted using the lowest dosage and titrated upward to prior dosages.

**Adverse Effect**

*More common -*
Loss of appetite; weight loss; diarrhea; nausea; vomiting

*Less common -*
Abdominal pain; pale skin; troubled breathing with activity; slow or irregular heartbeat (less than 50 beats per minute); light-headedness; dizziness or fainting; unusual tiredness or weakness; indigestion; headache; blood in urine; lower back pain; pain or burning while urinating; trouble sleeping; unable to sleep; sleepiness; sleeplessness; stuffy nose; unusual bleeding or bruising; unusual drowsiness; high or low blood pressure; tremor

**Symptoms of overdose**
Cramping; defecation or urination, uncontrolled; dizziness; rooling; fainting; increased sweating; low blood pressure; muscle weakness; seizures; slow heart beat; severe nausea or vomiting; slow or troubled breathing; tearing of the eyes; watering of the mouth

**Contraindications:**
Hypersensitivity to galantamine or any component of the formulation; severe liver dysfunction (Child-Pugh score 10-15); severe renal dysfunction (Clcr <9 mL/minute)

**Drug Interaction**

*Anesthesia:* Potential pharmacologic interaction (exaggerated response to succinylcholine-type muscle relaxants during surgery).

*Anticholinergics:* Potential pharmacologic interaction (antagonistic effects).

*Cholinomimetics and Other Cholinesterase Inhibitors:* Potential pharmacologic interaction (additive effects).

*Drugs Metabolized by Hepatic Microsomal (Cytochrome P-450) Enzymes:* Inhibitors or inducers of cytochrome P-450 (CYP) isoenzymes 3A4 or 2D6, potential pharmacokinetic interaction (altered galantamine metabolism).

*Amitriptyline, Fluoxetine, Fluvoxamine, Quinidine:* Pharmacokinetic interaction (decreased galantamine clearance).

*Cimetidine, Paroxetine:* Pharmacokinetic interaction (increased galantamine bioavailability).

*Erythromycin, Ketoconazole:* Pharmacokinetic interaction (increased area under the plasma galantamine concentration-time curve).

*Digoxin, Ranitidine, Warfarin:* Pharmacokinetic interaction unlikely.

**Drug Comparison**

1. Comparison of the different reversible inhibitors of acetylcholinesterase used in mild to moderate dementia in Alzheimer’s disease
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Side effects</th>
<th>Recommended dose (maintenance dose)</th>
<th>Price/ tab (in £)</th>
<th>Daily cost (in £)</th>
<th>Annual cost (in £)</th>
<th>Available dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept®) by Pfizer/Eisai</td>
<td>Prevents the breakdown of acetylcholine in the brain</td>
<td>Nausea, diarrhea, vomiting</td>
<td>5-10mg qd hs</td>
<td>5mg: 2.44</td>
<td>2.44-3.42</td>
<td>890.6-1248.3</td>
<td>Tablet</td>
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<td></td>
<td></td>
<td></td>
<td>10mg: 3.42</td>
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<td></td>
<td></td>
<td></td>
<td>4.8-7.2</td>
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<tr>
<td>Galantamine (Reminyl®) by Shire Pharmaceuticals and Janssen Cilag</td>
<td>Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain</td>
<td>Nausea, vomiting, diarrhea, weight loss</td>
<td>8-12mg bd</td>
<td>4mg: 0.975</td>
<td>Tab: 2.44-3.0</td>
<td>Tab: 890.6-1095</td>
<td>Tablet and oral solution</td>
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<td></td>
<td></td>
<td></td>
<td>8mg: 1.22</td>
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<td></td>
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<td></td>
<td>12mg: 1.5</td>
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<tr>
<td>Rivastigmine (Exelon®) by Novartis</td>
<td>Prevents the breakdown of acetylcholine and butyrylcholine</td>
<td>Nausea, vomiting, weight loss, upset stomach, muscle weakness</td>
<td>3-6mg bd</td>
<td>1.5mg: 1.215</td>
<td>Cap: 2.43</td>
<td>Cap: 886.95</td>
<td>Capsule and oral solution</td>
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<td></td>
<td></td>
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<td>3mg: 1.215</td>
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<td></td>
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<td>4.5mg: 1.215</td>
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<td>6mg: 1.215</td>
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<td></td>
<td>2mg/ml (soln): 0.972/ml</td>
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</tbody>
</table>

* No published study directly compares these drugs effectiveness. Because all four work in a similar way, it is not expected that switching from one of these drugs to another will produce significantly different results. So, all of the three reversible inhibitors of acetylcholinesterase are assumed to be equally effective. However, an AD patient may respond better to one drug than another.
2. Is Galantamine better than the other two reversible inhibitors of acetylcholinesterase?

**On cost-effectiveness basis**
As all of the three reversible inhibitors of acetylcholinesterase are considered to be equally effective, a lower cost indicates a higher cost-effectiveness. As mild to moderate AD patients need to take reversible inhibitors of acetylcholinesterase throughout their life, we compare their annual costs rather than their daily costs. For mild AD patients, we compare their lowest maintenance doses. Rivastigmine becomes the best among them. For moderate AD patients, we compare their highest maintenance doses. Rivastigmine becomes the best among them again.

**On patient compliance basis**
Donepezil is taken once daily but Galantamine and Rivastigmine are taken twice daily, so, Donepezil becomes the best choice as it is taken least frequently. Donepezil causes the least amount of side effects and may lead to better compliance.

**On the ease of administration basis**
Both galantamine and rivastigmine have oral solution form which can be taken more easily than tablets or capsules. Rivastigmine is cheaper than galantamine. So, rivastigmine is better.

**On the mode of action basis**
All three reversible inhibitors of acetylcholinesterase prevent the breakdown of acetylcholine, but galantamine has extra mode of action to stimulate nicotinic receptors to release more acetylcholine in the brain. As galantamine is a new drug, so, more clinical trials have to be done before confirming the extra benefits from this mode of action.

Reference:


