PRODUCT NAME
REMINYL® (galantamine hydrobromide)

DOSAGE FORMS AND STRENGTHS
Prolonged-release capsules for oral use
8 mg capsules
White opaque, size 4 hard gelatin capsules with the inscription "GAL 8", containing white to off-white pellets. Each capsule contains galantamine hydrobromide, equivalent to 8 mg galantamine base.

16 mg capsules
Pink opaque, size 2 hard gelatin capsules with the inscription "GAL 16", containing white to off-white pellets. Each capsule contains galantamine hydrobromide, equivalent to 16 mg galantamine base.

24 mg capsules
Caramel opaque, size 1 hard gelatin capsules with the inscription "GAL 24", containing white to off-white pellets. Each capsule contains galantamine hydrobromide, equivalent to 24 mg galantamine base.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
REMINYL® is indicated for the treatment of mild to moderately severe dementia of the Alzheimer type.

Dosage and Administration
Dosage – Adults
Ensure adequate fluid intake during treatment.

Starting dose
The recommended starting dose of REMINYL® prolonged-release capsules is 8 mg once daily for 4 weeks.

The dose of REMINYL® should be gradually increased to the maintenance dose to minimize side effects.

Maintenance dose
The initial maintenance dose is 16 mg/day (16 mg once a day with capsules) and patients should be maintained on 16 mg/day for at least 4 weeks. An increase to the maximum recommended maintenance dose of 24 mg/day (24 mg once a day with capsules) should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.

Treatment withdrawal
There is no rebound effect after abrupt discontinuation of treatment (e.g. in preparation for surgery).

Re-initiation of therapy
If the treatment is interrupted for longer than several days, treatment should be re-initiated with the lowest daily dose and gradually increased to the maximum tolerated dose to achieve the desired clinical effect. The incidence and severity of adverse events are generally related to the higher doses of REMINYL®.

Special populations
Pediatrics
Use of REMINYL® in children is not recommended. No data on the use of REMINYL® in pediatric patients are available.

Renal impairment
Galantamine plasma concentrations may be increased in patients with moderate (creatinine clearance = 52-104 mL/min) to severe (creatinine clearance = 9-51 mL/min) renal impairment.

For patients with a creatinine clearance >9 mL/min, no dosage adjustment is required (see *Pharmacokinetic Properties – Special populations*).

The use of REMINYL® is not recommended in patients with creatinine clearance less than 9 mL/min because no data are available.

Hepatic impairment
Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment.

In patients with moderately impaired hepatic function (Child-Pugh score 7-9), for prolonged-release capsules, based on pharmacokinetic modeling, dosing should begin with 8 mg every other day for at least one week, preferably taken in the morning. Thereafter, patients should proceed with 8 mg once daily for prolonged-release capsules for at least four weeks. In these patients, total daily doses should not exceed 16 mg.

No dosage adjustment is required for patients with mild hepatic impairment. In patients with severe hepatic impairment (Child-Pugh score >9), the use of REMINYL® is not recommended.

Concomitant treatment
In patients treated with potent CYP2D6 or CYP3A4 inhibitors (e.g. ketoconazole), dose reductions can be considered (see *Interactions – Other drugs affecting the metabolism of galantamine*).

Administration
REMINYL® is administered orally.

REMINYL® prolonged-release capsules should be administered once daily in the morning, preferably with food.

Contraindications
REMINYL® should not be administered to patients with a known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulations.

Warnings and Precautions
Types of dementia other than Alzheimer's dementia
REMINYL® is indicated for patients with mild to moderately severe dementia of the Alzheimer's type. The benefit of REMINYL® in patients with other types of dementia or other types of memory impairment has not been demonstrated.

Serious skin reactions
Serious skin reactions (Stevens Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in patients receiving REMINYL® (see *Adverse Reactions*). It is recommended that patients be informed about the signs of serious skin reactions, and that use of REMINYL® be discontinued at the first appearance of skin rash.

Weight monitoring
Patients with Alzheimer's disease lose weight. Treatment with cholinesterase inhibitors, including galantamine, has been associated with weight loss in these patients. During therapy, patient's weight should be monitored.

Conditions requiring caution
As with other cholinomimetics, REMINYL® should be given with caution in the following conditions:

Cardiovascular Conditions: Because of their pharmacological action, cholinomimetics may have vagotonic effects on heart rate, including bradycardia and all types of atrioventricular node block (see *Adverse Reactions*). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or who use drugs that significantly reduce heart rate concomitantly, such as digoxin and beta-blockers. In clinical trials, use of REMINYL® has been associated with syncope, and rarely with severe bradycardia.

There have been reports of QTc prolongation in patients using therapeutic doses of galantamine and of *torsade de pointes* in association with overdoses (see *Overdose*). Galantamine should therefore be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Gastrointestinal Conditions: Patients at increased risk of developing peptic ulcers, e.g. those with a history of ulcer disease or those predisposed to these conditions, including those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS), should be monitored for symptoms. However, clinical studies with REMINYL® showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. The use of REMINYL® is not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Neurological Conditions: Convulsions have been reported with REMINYL® (see *Adverse Reactions – Postmarketing data*). Seizure activity may also be a manifestation of Alzheimer's disease. An increase in cholinergic tone may worsen symptoms related to extrapyramidal disorders (see *Adverse Reactions – Postmarketing data*).

Pulmonary Conditions: Because of their cholinomimetic actions, cholinomimetics should be prescribed with care for patients with a history of severe asthma or obstructive pulmonary disease.

Genitourinary: The use of REMINYL® is not recommended in patients with urinary outflow obstruction or recovering from bladder surgery.

Safety in Subjects with Mild Cognitive Impairment (MCI)

REMINYL® is not indicated for individuals with mild cognitive impairment (MCI), i.e., those who demonstrate isolated memory impairment greater than expected for their age and education, but do not meet criteria for Alzheimer's disease.

Two, 2-year controlled trials in subjects with MCI did not meet dual primary efficacy outcomes. Although mortality in both treatment arms was low, more deaths were initially recorded in subjects randomized to galantamine than to placebo, but the incidence of serious adverse events was identical between treatment groups. The deaths were due to various causes that are not unexpected in an elderly population. When data retrieved from the large proportion of patients who discontinued prior to completion of the double-blind period was included, there was no evidence of an increasing risk of death in REMINYL®-treated subjects over time. More subjects from the placebo than the galantamine group discontinued prior to death, which may account for the difference in mortality initially recorded.

The MCI study results are discrepant from those observed in studies of Alzheimer's disease. In pooled studies in Alzheimer's disease (n=4614), the mortality rate was numerically higher in the placebo than the REMINYL® group.

Interactions

Pharmacokinetic interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine.

Inhibition of gastric acid secretion will not impair the absorption of galantamine.

Other drugs affecting the metabolism of galantamine

Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC only increased approximately 10%. Population PK analysis for patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline, fluoxetine, fluvoxamine, paroxetine and quinidine, known inhibitors of CYP2D6.

Therefore, during initiation of treatment with potent inhibitors of CYP2D6 or CYP3A4 patients may experience an increased incidence of cholinergic side effects, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the galantamine maintenance dose can be considered (see *Dosage and Administration – Special populations*).

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, at a dose of 10 mg/daily for 2 days followed by 10 mg twice a day for 12 days had no effect on the pharmacokinetics of galantamine 16 mg/day at steady state.

Effect of galantamine on the metabolism of other drugs

Therapeutic doses of galantamine (12 mg twice a day) had no effect on the kinetics of digoxin and warfarin. Galantamine did not affect the increased prothrombin time induced by warfarin.

In vitro studies indicated that the inhibition potential of galantamine with respect to the major forms of human cytochrome P450 is very low.

Pharmacodynamic interactions

Because of its mechanism of action, galantamine should not be given concomitantly with other cholinomimetics. Galantamine antagonizes the effect of anticholinergic medication. As expected with cholinomimetics, a pharmacodynamic interaction is possible with drugs that significantly reduce the heart rate (e.g. digoxin and beta blockers).

Galantamine, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Pregnancy and Breast-Feeding

Pregnancy

Reproduction studies conducted in pregnant rats at doses up to 16 mg/kg (or about 25 times the human therapeutic dose) and in pregnant rabbits up to 40 mg/kg (or about 63 times the human therapeutic dose) did not show any evidence of a teratogenic potential. A non-significant increase in the incidence of minor skeletal abnormalities was noted at a dose of 16 mg/kg in rats.

No studies are available on the use of REMINYL® in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether REMINYL® is excreted in human breast milk and there are no studies in lactating women. Therefore, women on REMINYL® should not breast-feed.

Effects on Ability to Drive and Use Machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, like other cholinomimetics, REMINYL® may cause adverse reactions (such as dizziness and somnolence), which could affect the ability to drive or use machines, especially during the first weeks after initiation of treatment (see *Adverse Reactions*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of galantamine hydrobromide based on the comprehensive assessment of the available adverse event information. A causal relationship with galantamine hydrobromide usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Double-blind data –adverse drug reactions reported at ≥1% frequency

The safety of REMINYL® was evaluated in 6502 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in8 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of REMINYL®-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Reactions Reported by ≥1% of REMINYL®-Treated Subjects in 8 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Reaction	**REMINYL® (n=3956)** **%**	**Placebo (n=2546)** **%**
Metabolism and Nutrition Disorders		
Decreased appetite	7.4	2.1
Psychiatric Disorders		
Depression	3.6	2.3
Nervous System Disorders		
Dizziness	6.8	2.9

Table 1. Adverse Reactions Reported by ≥1% of REMINYL®-Treated Subjects in 8 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse Reaction	**REMINYL® (n=3956) %**	**Placebo (n=2546) %**
Headache	7.1	5.5
Tremor	1.6	0.7
Syncope	1.4	0.6
Lethargy	1.3	0.4
Somnolence	1.5	0.8
Cardiac Disorders		
Bradycardia	1.0	0.3
Gastrointestinal Disorders		
Nausea	20.7	5.5
Vomiting	10.5	2.3
Diarrhea	7.4	4.9
Abdominal pain	2.0	0.6
Abdominal pain upper	1.9	1.4
Dyspepsia	1.5	1.0
Abdominal discomfort	2.1	0.7
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	1.2	0.5
General Disorders and Administration Site Conditions		
Fatigue	3.5	1.8
Asthenia	2.0	1.5
Malaise	1.1	0.5
Investigations		
Weight decreased	4.7	1.5
Injury, Poisoning and Procedural Complications		
Fall	3.9	3.0
Laceration	1.1	0.5

In a randomized, double-blind, placebo-controlled clinical trial, the safety profile of once-daily treatment with REMINYL® prolonged-release capsules was similar in frequency and nature to that seen with tablets.

Nausea and vomiting, the most frequent adverse reactions, occurred mainly during titration periods, lasted less than a week in most cases and the majority of patients had one episode. Prescription of anti-emetics and ensuring adequate fluid intake may be useful in these instances.

Double-blind and open-label data – adverse drug reactions reported at <1% frequency

In addition to double-blind clinical trials, the safety of REMINYL® was evaluated in 1454 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in 5 open-label clinical trials.

Additional adverse reactions not reported in Table 1 that occurred in <1% of REMINYL®-treated subjects (n=5410) in the 8 double-blind and 5 open-label clinical datasets are listed in Table 2.

Table 2. Adverse Reactions Reported by <1% of REMINYL®-Treated Subjects in Either Double-Blind or Open-Label Clinical Trials

System Organ Class Adverse Reaction	**REMINYL® (n=5410) %**
Metabolism and Nutrition Disorders	
Dehydration	0.96
Nervous System Disorders	
Dysgeusia	0.31
Hypersomnia	0.55
Paresthesia	0.33
Eye Disorders	
Vision blurred	0.31
Cardiac Disorders	
Atrioventricular block first degree	0.30
Palpitations	0.41
Sinus bradycardia	0.55
Supraventricular extrasystoles	0.46
Vascular Disorders	
Flushing	0.24
Hypotension	0.52
Gastrointestinal Disorders	
Retching	0.22
Skin and Subcutaneous Tissue Disorders	
Hyperhydrosis	0.85
Musculoskeletal and Connective Tissue Disorders	
Muscular weakness	0.61

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience. Table 3 provides adverse reaction frequencies according to the following convention:

Very common	≥ 1/10 (≥10%)
Common	≥ 1/100 and < 1/10 (≥1% and <10%)
Uncommon	≥ 1/ 1000 and < 1/100 (≥0.1% and <1%)
Rare	≥ 1/10000 and < 1/1000 (≥0.01% and <0.1%)
Very rare	< 1/10000 (<0.01%), including isolated reports

Not known Cannot be estimated from the available data.

Table 3. Adverse Reactions Identified During Postmarketing Experience with REMINYL®	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Clinical Trials with REMINYL®**
Immune System Disorders	
Hypersensitivity	*Uncommon*
Psychiatric Disorders	
Hallucination	*Common*
Hallucination visual	*Uncommon*
Hallucination auditory	*Uncommon*
Nervous System Disorders	
Convulsion	*Uncommon*
Extrapyramidal disorder	*Uncommon*
Ear and Labyrinth Disorders	
Tinnitus	*Uncommon*
Cardiac Disorders	
Atrioventricular block complete	*Rare*
Vascular Disorders	
Hypertension	*Common*
Hepatobiliary Disorders	
Hepatitis	*Rare*
Skin and subcutaneous tissue disorders	
Stevens Johnson Syndrome,	*Not known*
Acute generalized exanthematous pustulosis	*Not known*
Erythema multiforme	*Not known*
Investigations	
Hepatic enzyme increased	*Uncommon*

Overdose

Symptoms and signs

Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the signs of a

cholinergic crisis may develop: severe nausea, vomiting, gastro-intestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, collapse and convulsions. Increasing muscle weakness together with tracheal hypersecretions and bronchospasm, may lead to vital airway compromise.

There have been post-marketing reports of Torsade de Pointes, QT prolongation, bradycardia, ventricular tachycardia and brief loss of consciousness in association with inadvertent overdoses of galantamine. In one case where the dose was known, eight 4mg tablets (32 mg total) were ingested on a single day.

Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 mL) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

Treatment
As in any case of overdose, general supportive measures should be used. In severe cases, anticholinergics such as atropine can be used as a general antidote for cholinomimetics. An initial dose of 0.5 to 1.0 mg intravenously is recommended, with subsequent doses based on the clinical response.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Antidementia drugs; ATC-code : N06D A04.

Mechanism of action
Galantamine, a tertiary alkaloid is a selective, competitive and reversible inhibitor of acetylcholinesterase. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. As a consequence, an increased activity in the cholinergic system associated with improved cognitive function can be achieved in patients with dementia of the Alzheimer type.

Clinical studies
The dosages of REMINYL® shown to be effective in controlled clinical trials in Alzheimer's disease were 16, 24 and 32 mg/day. Of these doses, 16 and 24 mg/day were determined to have the best benefit/risk relationship and are the recommended doses.

Galantamine's efficacy has been studied using four specific outcome measures: the ADAS-cog (a performance based measure of cognition), the CIBIC-plus (a global assessment by an independent physician based on a clinical interview with the patient and caregiver), several measurements of the activities of daily living and the Neuropsychiatric Inventory (NPI, a scale that measures behavioral disturbances).

In clinical studies, performance of galantamine treated patients on the ADAS-cog (see Figure) and CIBIC-plus was consistently statistically significantly better than that of patients who were on placebo. Patients who were treated for 6 months with galantamine had ADAS-cog scores that were significantly improved compared to their baseline scores. Compared to the untreated patients there was a substantial and sustained benefit in cognitive functioning. Galantamine treatment also significantly preserved the activities of daily living, such as dressing, hygiene, meal preparation. These were assessed using the Disability Assessment in Dementia (the DAD) and the Alzheimer's Disease Cooperative Study (ADCS)-ADL-Inventory, caregiver-rated assessments. Galantamine doses of 16 and 24 mg daily maintained the NPI score throughout the observation period whereas the score of the placebo patients clearly deteriorated, as a result of the emergence of behavioral disturbances.

Figure 1. Mean (± SE) change from baseline in ADAS-cog/11 score over time (observed data) (pooled data GAL-USA-1 and GAL-INT-1)

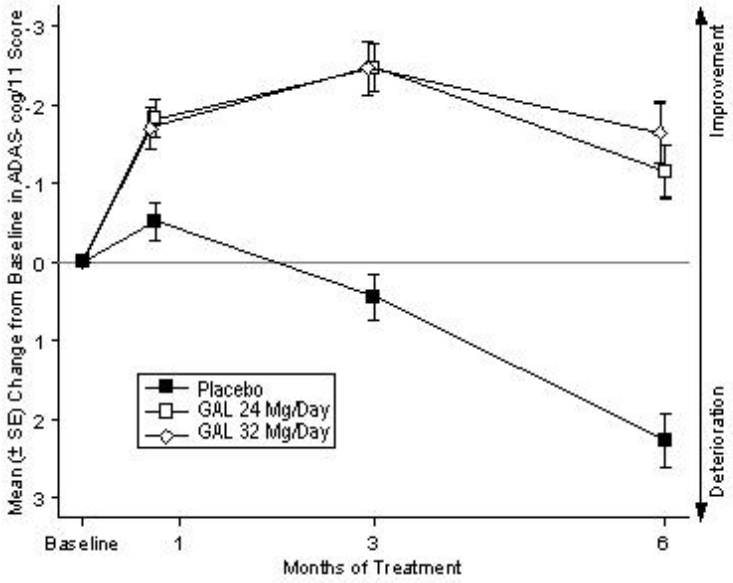
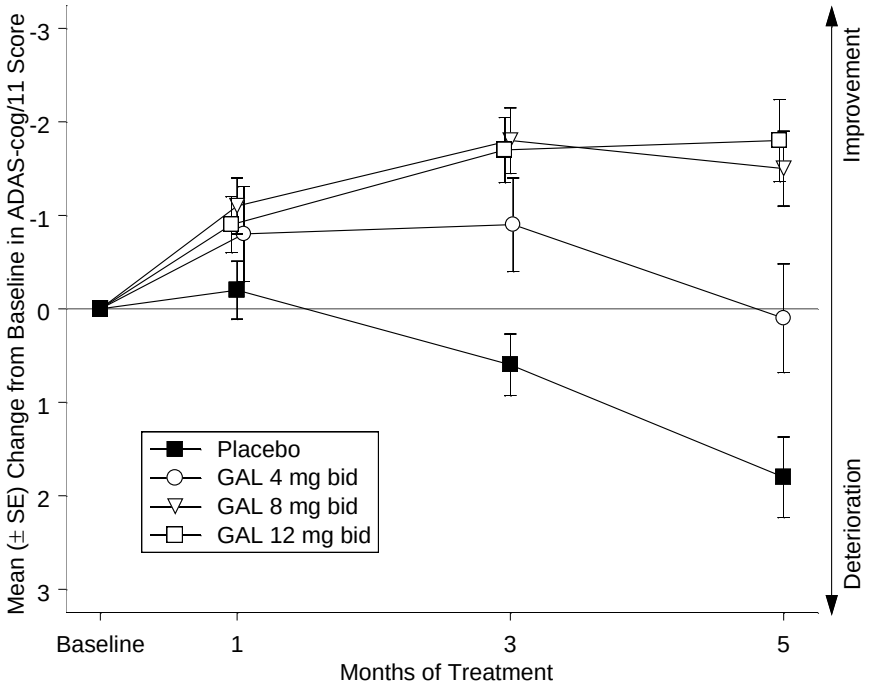


Figure 2. Mean (± SE) change from baseline in ADAS-cog/11 score over time (all patients, observed data) (GAL-USA-10)



Long-term treatment (combination of 6 months double-blind followed by 6 months open treatment) suggested that patients' cognitive and functional performance was maintained for a full year.

The results of a 26-week double-blind placebo-controlled trial, in which patents with vascular dementia and patients with Alzheimer's disease and concomitant cerebrovascular disease ("Mixed dementia") were included indicate that the symptomatic effect of galantamine is maintained in patients with Alzheimer's disease and concomitant cerebrovascular disease. In a post-hoc subgroup analysis, no statistically significant effect was observed in the subgroup of patients with vascular dementia alone.

In a second 26-week placebo-controlled trial in patients with probable vascular dementia, no clinical benefit of galantamine was demonstrated.

The efficacy of REMINYL® prolonged-release capsules was studied in a randomized, double-blind, placebo-controlled trial in Alzheimer's disease. Patients received galantamine 8 mg/day for 4 weeks, followed by galantamine 16 mg/day for 4 weeks. At week 8, the dose could be increased to 24 mg/day based on safety and tolerability, and could be reduced to 16 mg/day at week 12. The dose chosen at week 12 was fixed for the remainder of the 6 months. In the protocol-specified primary efficacy analysis for the two endpoints (ADAS-cog/11 and CIBIC-plus) at Month 6 simultaneously, REMINYL® prolonged-release showed a statistically significant improvement over placebo for ADAS-cog/11 only. In addition, REMINYL® prolonged-release was statistically

significantly better than placebo in improving activities of daily living (ADCS-ADL), a key secondary efficacy measure. Efficacy results were similar for REMINYL® prolonged-release capsules and REMINYL® tablets, which served as an active control in this study.

Long-term (2-year) efficacy and safety in mild to moderately severe Alzheimer's disease

A randomized, double-blind, placebo-controlled, parallel group, multi-center study evaluated the long-term (2-year) efficacy and safety of galantamine prolonged-release capsules in the treatment of patients with mild to moderately-severe Alzheimer's disease. One thousand and twenty three patients were randomized to the placebo group, and 1028 to the galantamine group. Demographic and baseline characteristics were similar between the groups. The majority of patients were female (65%) and white (99.9%). The median age was 74 years, and baseline Mini-Mental State Examination (MMSE) score was 19.

On the primary efficacy endpoint (defined as change from baseline in the MMSE score at Month 24), there was a significantly less cognitive impairment in the galantamine group compared with placebo in the change from baseline in MMSE at Month 24 (-1.41 versus -2.14; $p<0.001$). On the key secondary efficacy endpoints (defined as change in MMSE at Month 6 and change in DAD score at Month 24), there was significantly greater improvement in change from baseline in MMSE at Month 6 in the galantamine group compared with placebo (mean change of 0.15 versus -0.28; $p<0.001$) and significantly less impairment in the DAD score at Month 24 in the galantamine group compared to placebo (-8.2 versus -10.8; $p=0.002$).

On the primary safety endpoint (mortality), there was a total of 89 deaths; 56 (5.5%) deaths in the placebo group and 33 (3.2%) deaths in the galantamine group. This represents a significantly higher rate of death in the placebo group compared with galantamine [hazard ratio and 95% confidence intervals of 0.58 (0.37 – 0.89) ($p=0.011$)].

Mild cognitive impairment (MCI)

Two, 2-year controlled trials in subjects with MCI did not meet dual primary efficacy outcomes. Although mortality was low (0.7%), more deaths were initially recorded in subjects randomized to galantamine (13/1026) than to placebo (1/1022), but the incidence of serious adverse events was identical (19%) between treatment groups.

The 24-month intent-to-treat analysis recorded 20 deaths among subjects randomised to placebo compared to 34 deaths recorded among subjects randomised to galantamine (relative risk [95% CI] = 1.70 [1.00, 2.90]; $p = 0.051$. Of subjects who died within the protocol-specified period of 30 days of discontinuing double-blind study medication, there were 14 in the galantamine group and 3 in the placebo group (relative risk [95% CI] = 4.08 [1.57,10.57]; $p = 0.004$). Thirteen deaths in the placebo group and 20 deaths in the galantamine group were found to be directly related to adverse events that occurred while the subjects were exposed to double-blind study drug (relative risk [95% CI] = 1.54 (0.78, 3.04); $p = 0.218$.

More placebo-treated than galantamine-treated subjects discontinued prior to death, which may have accounted for the difference in mortality initially recorded. When data retrieved from the large proportion of patients in both treatment groups who discontinued prior to completion of the double-blind period (GAL-COG-3002) were included, a total of 102 deaths were identified, 56 in the galantamine group and 46 in the placebo group (relative risk [95% CI] = 1.24 [0.84,1.83]; p = 0.274).

The deaths were due to various causes that were not unexpected in an elderly population, with about half of the deaths in both groups due to vascular causes.

Pharmacokinetic Properties

Absorption

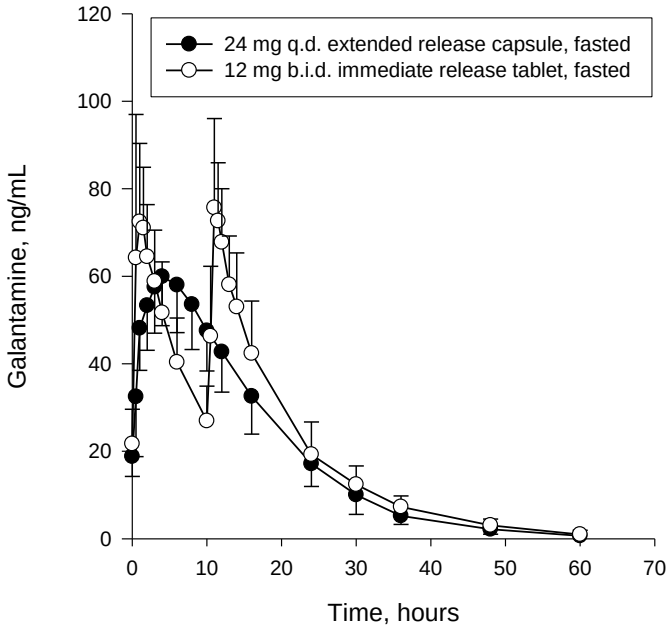
After oral intake of a single dose of 8 mg galantamine as tablets, absorption is rapid, with a peak plasma concentration of 43 ± 13 ng/mL, which is reached after 1.2 hours, and a mean AUC_{∞} of 427 ± 102 ng.h/mL. The absolute oral bioavailability of galantamine is 88.5%. Oral intake of galantamine tablets with food slows down its rate of absorption (C_{max} reduced by about 25%), but does not affect the extent to which it is absorbed (AUC).

After repeated oral dosing of 12 mg galantamine twice a day as tablets, mean trough and peak plasma concentrations fluctuated between 30 and 90 ng/mL. The pharmacokinetics of galantamine are linear in the dose range 4-16 mg twice a day.

Bioavailability of immediate-release versus prolonged-release formulations

In a steady-state bioavailability study, REMINYL® prolonged-release capsules, 24 mg once daily, were shown to be bioequivalent to the 12 mg twice-daily immediate-release tablets with respect to AUC_{24h} and C_{min}. The C_{max} value of the 24 mg once-daily prolonged-release capsule, which is reached after 4.4 hours, was about 24% lower than that of the 12 mg twice-daily immediate-release tablet. Food had no effect on the steady-state bioavailability of the 24 mg prolonged-release capsules. In a dose-proportionality study of REMINYL® prolonged-release capsules in healthy elderly and younger adult subjects, steady-state plasma concentrations were achieved within 6 days at all doses (8 mg, 16 mg, and 24 mg) in both age groups. Steady-state pharmacokinetics were dose-proportional within the studied dose range of 8 mg to 24 mg in both age groups.

Figure 3. Comparative Linear Plot of Mean Galantamine Plasma Concentration-Time Profiles



Distribution

Galantamine has a moderate volume of distribution (average Vd_{ss} of 175 l).

The plasma protein binding of galantamine is low: 17.7 ± 0.8%. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins in only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.17.

Metabolism

Major metabolic pathways were N-oxidation, N-demethylation, O-demethylation, glucuronidation and epimerization. O-demethylation was far more important in extensive metabolizers of CYP2D6. The levels of excretion of total radioactivity in urine and feces were not different between poor and extensive metabolizers. *In vitro* studies confirmed that cytochrome P450 2D6 and 3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine.

In plasma from poor and extensive metabolizers, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In plasma from extensive metabolizers, the glucuronide of O-desmethylgalantamine was also important.

None of the active metabolites of galantamine (norgalantamine, O-desmethylgalantamine and O-desmethyl-norgalantamine) could be detected in their unconjugated form in plasma from poor or extensive metabolisers after single dosing. Norgalantamine was detectable in plasma from patients after multiple dosing, but did not represent more than 10% of the galantamine levels.

Elimination

Galantamine is a low-clearance drug (plasma clearance of approximately 300 mL/min). The elimination of galantamine is bi-exponential, with a terminal half-life in the order of 7-8 h.

Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 90-97% of the radioactivity was recovered in urine and 2.2-6.3% in the feces. After i.v. and oral administration, 18-22% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 mL/min, which represents 20-25% of the total plasma clearance.

Special populations

Renal impairment

The disposition of galantamine was studied in young subjects with varying degrees of renal function. Elimination of galantamine decreased with decreasing creatinine clearance. Plasma concentrations of galantamine increased in subjects with impaired renal function by 38% in moderate (creatinine clearance = 52-104 mL/min) or 67% in severe renal impairment (creatinine clearance = 9-51 mL/min), compared to age and weight-matched healthy subjects (creatinine clearance = ≥121 mL/min). A population pharmacokinetic analysis and simulations indicate that no dose-adjustments are needed in Alzheimer patients with renal impairment provided that the creatinine clearance is at least 9 mL/min (see *Dosage and Administration – Special populations*) as the galantamine clearance is lower in the Alzheimer population.

Hepatic impairment

The pharmacokinetics of galantamine in subjects with mild hepatic impairment (Child-Pugh score of 5-6) were comparable to those in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% (see *Dosage and Administration – Special populations*).

Characteristics in patients with Alzheimer's disease

Data from clinical trials in patients indicate that the plasma concentrations of galantamine in patients with Alzheimer's disease are 30-40% higher than in healthy young subjects.

NON-CLINICAL INFORMATION

All other preclinical safety data relevant to the prescriber have been included in the appropriate sections.

PHARMACEUTICAL INFORMATION

List of Excipients

Diethyl phthalate
Ethylcellulose
Gelatin
Hypromellose
Maize starch
Macrogol

Red ferric oxide (E172) *(16mg and 24mg capsule)*
Sucrose
Titanium dioxide (E171)
Yellow ferric oxide (E172) (*24mg capsule*)

Incompatibilities
Not applicable.

Shelf Life
See expiry date on the outer pack.

Storage Conditions
Do not store above 30°C.
Keep out of reach of children.

Nature and Contents of Container
The prolonged-release capsules are packaged in PVC-PE-PVDC/Alu blister that holds 7 capsules.
Blisters are packed in a cardboard box.
Available pack sizes: 8 mg 28 capsules, 16 mg 28 capsules and 24 mg 28 capsules.

PRODUCT REGISTRANT
Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
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BATCH RELEASER
Janssen-Cilag S.p.A., Via C. Janssen,
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