REMINYL® CAPSULES

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

REMINYL® 8 mg, 16 mg, 24 mg modified release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release capsule contains galantamine hydrobromide equivalent to 8, 16 or 24 mg of galantamine base as the active ingredient.

Excipient(s) with known effect
Sucrose (contained in sugar spheres)

For the full list of excipients, see section **6.1**.

3. PHARMACEUTICAL FORM

- REMINYL 8 mg modified release capsules are white opaque, size 4 hard gelatin capsules with the inscription “G8”, containing white to off-white pellets.
- REMINYL 16 mg modified release capsules are pink opaque, size 2 hard gelatin capsules with the inscription “G16”, containing white to off-white pellets.
- REMINYL 24 mg modified release capsules are caramel opaque, size 1 hard gelatin capsules with the inscription “G24”, containing white to off-white pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REMINYL is indicated for the treatment of mild to moderately severe dementia of the Alzheimer type.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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

Starting dose

The recommended starting dose is 8 mg a day for four weeks.

Maintenance dose

- The initial maintenance dose is 16 mg a day and patients should be maintained on this dose for at least 4 weeks.

- An increase to the maximum recommended maintenance dose of 24 mg a day should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.
- There is no rebound effect after abrupt discontinuation of treatment, for example, prior to surgery.

Re-initiation of therapy

If 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.

In patients co-treated with ketoconazole or potent inhibitors of cytochrome P450 2D6, dose reductions can be considered (see section **4.5**).

Special populations

Use in patients with renal and hepatic impairment

Plasma levels of galantamine may be increased in patients with moderate to severe hepatic or renal impairment.

In patients with moderately impaired hepatic function, for modified release capsules, based on pharmacokinetic modelling, dosing should begin with 8 mg every other day for at least one week, preferably taken in the morning. Then dosage should be increased to 8 mg once daily for modified release capsules for at least four weeks. In these patients, total daily doses should not exceed 16 mg a day.

In patients with severe hepatic impairment (Child-Pugh score greater than 9), the use of REMINYL is contraindicated (see section **4.3**).

No dosage adjustment is required for patients with mild hepatic impairment.

For patients with a creatinine clearance greater than 9 mL/min, no dosage adjustment is required. In patients with severe renal impairment (creatinine clearance less than 9 mL/min), the use of REMINYL is contraindicated (see section **4.3**).

Paediatric population

Use of REMINYL in children is not recommended. No data on the use of REMINYL in paediatric patients are available.

Method of administration

REMINYL modified release capsules should be administered once daily in the morning, preferably with food. Ensure adequate fluid intake during treatment.

4.3 CONTRAINDICATIONS

REMINYL is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or any excipients used in the formulations (see section **6.1**).

Since no data are available on the use of REMINYL in patients with severe hepatic impairment (Child-Pugh score greater than 9) or severe renal impairment (creatinine clearance less than 9 mL/min), REMINYL is contraindicated in these populations.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in other types of dementia

The benefit of REMINYL in patients with other types of dementia or other types of memory impairment has not been demonstrated. REMINYL is indicated for patients with mild to moderately severe dementia of the Alzheimer type.

Serious skin reactions

Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in patients receiving REMINYL (see section **4.8**). 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.

Use with caution in the following circumstances

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 section **4.8**). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or who concomitantly use medicines that significantly reduce heart rate (eg digoxin and beta blockers) (see section **4.5**). Cholinomimetics should therefore be given with caution to patients in the immediate post-myocardial infarction period, who have new-onset atrial fibrillation, who have second-degree heart block or greater, who have unstable angina pectoris, uncorrected electrolyte disturbance (eg hyperkalaemia, hypokalaemia) or congestive cardiac failure, especially NYHA group III-IV. In clinical trials, use of REMINYL has been associated with syncope and rarely with severe bradycardia.

Gastrointestinal conditions: Patients at increased risk of developing peptic ulcers, (eg 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 gastrointestinal obstruction or recovering from gastrointestinal surgery.

Neurological conditions: Convulsions have been reported with REMINYL (see section **4.8**). Seizure activity may also be a manifestation of Alzheimer's disease. An increase in

cholinergic tone may worsen symptoms related to extrapyramidal disorders (see section **4.8**), including Parkinsonian symptoms.

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. Similarly, caution should be exercised in treating patients with active pneumonia.

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

Mild cognitive impairment

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 current diagnostic criteria for Alzheimer's disease.

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 REMINYL (13/1026) than to placebo (1/1022), but the incidence of serious adverse events was identical (19%) between treatment groups.

Because of this finding a retrieved drop out study was conducted to determine the mortality status of all subjects who participated in the two studies. On completion of this study with vital status recorded on greater than 98% of enrolled subjects, a total of 46 deaths were recorded on subjects randomised to placebo compared to 56 deaths recorded with REMINYL (relative risk [95% CI] = 1.24 [0.84,1.83]; p = 0.274). The 24-month intent-to-treat analysis recorded 20 deaths among subjects randomised to placebo compared to 34 deaths recorded among subjects randomised to REMINYL (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 REMINYL group and 3 in the placebo group (relative risk [95% CI] = 4.08 [1.57,10.57]; p = 0.004). The deaths were due to various causes which could be expected in an elderly population; about half of REMINYL and placebo deaths appeared to result from various vascular causes. There was no evidence of an increasing risk of death in REMINYL-treated subjects over time.

More placebo-treated than REMINYL-treated subjects discontinued prior to death. Thirteen deaths in the placebo group and 20 deaths in the REMINYL 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).

The MCI study results are discrepant from those observed in studies of Alzheimer's disease. When the Alzheimer's disease and other dementia studies were pooled (n=6000), the mortality rate in the placebo group numerically exceeded that in the REMINYL group.

There is no evidence of an increased risk of mortality due to REMINYL in the current approved indication of mild to moderately severe Alzheimer's disease.

Use in patients with hepatic impairment

Plasma levels of galantamine may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function, dosage should be adjusted (see section **4.2**).

Since no data are available on the use of REMINYL in patients with severe hepatic impairment, its use is contraindicated (see section **4.3**).

Use in patients with renal impairment

For patients with a creatinine clearance greater than 9 mL/min, no dosage adjustment is required. In patients with severe renal impairment (creatinine clearance less than 9 mL/min), the use of REMINYL is contraindicated (see section **4.3**).

Use in children

Use of REMINYL in children is not recommended. No data on the use of REMINYL in paediatric patients are available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Pharmacodynamic Interactions

Because of its mechanism of action, REMINYL should not be given concomitantly with other cholinomimetics. REMINYL antagonises the effect of anticholinergic medication. As expected with cholinomimetics, a pharmacodynamic interaction is possible with medicines that significantly reduce the heart rate (eg digoxin and beta blockers). REMINYL, as a cholinomimetic, is also likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Pharmacokinetics Interactions

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

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. This may explain why no major interactions were observed.

Other medicines affecting the metabolism of galantamine

Formal drug interaction studies showed an increase in galantamine bioavailability of about 40% during co-administration of paroxetine (a potent CYP2D6 inhibitor) and of 30% and 12% during co-administration with ketoconazole and erythromycin (both CYP3A4 inhibitors). Therefore, during initiation of treatment with potent inhibitors of CYP2D6 (eg quinidine, paroxetine, fluoxetine or fluvoxamine) or CYP3A4 (eg ketoconazole), patients may experience an increased incidence of cholinergic side effects, predominantly nausea and vomiting. Based on tolerability, a reduction of the galantamine maintenance dose can be considered.

Memantine, an N-methyl-D-asparate (NMDA) receptor antagonist, at a dose of 10 mg/daily for 2 days followed by 10 mg BID 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 medicines

Therapeutic doses of galantamine (12 mg twice daily) 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 and is not considered clinically relevant.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category B1.

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

Reproduction studies in pregnant rats and rabbits at respective exposure levels up to 5 and 3 times higher than that in humans at the maximum recommended dose (based on plasma AUC values), did not show any evidence of teratogenic potential. Minor skeletal abnormalities and decreased birth weight were seen at the highest dose in rats.

Breast-feeding

It is not known whether REMINYL is excreted in human breast milk and no studies have been performed in lactating women. Therefore, women taking REMINYL should not breastfeed.

Fertility

Galantamine had no effect on the fertility in rats at plasma $AUC_{0\text{-}24h}$ levels 5 times higher than those in humans at the maximum recommended dose.

4.7 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. As with other cholinomimetics, REMINYL may cause dizziness and somnolence, especially during the first weeks after initiation of treatment. This could affect the ability to drive or use machines.

4.8 UNDESIRABLE EFFECTS

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 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 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 in 8 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
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 extended 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 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 2 that occurred in <1% of REMINYL-treated subjects in the 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
Metabolism and Nutrition Disorders Dehydration **Nervous System Disorders** Dysgeusia, Hypersomnia, Paresthesia **Eye Disorders** Vision blurred **Cardiac Disorders** Atrioventricular block first degree, Palpitations, Sinus bradycardia, Supraventricular extrasystoles **Vascular Disorders** Flushing, Hypotension **Gastrointestinal Disorders** Retching **Skin and Subcutaneous Tissue Disorders** Hyperhydrosis **Musculoskeletal and Connective Tissue Disorders** Muscular weakness

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). In each table, the frequencies are provided according to the following convention:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/ 1000 and < 1/100

Rare ≥ 1/10000 and < 1/1000
Very rare < 1/10000, including isolated reports.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Symptoms

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, gastrointestinal 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 4 mg tablets (32mg 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: psychoanaleptics, anti-dementia drugs; ATC code: N06DA04

Mechanism of action

REMINYL (galantamine) is a cholinomimetic with a dual mechanism of action. REMINYL is a reversible inhibitor of the enzyme acetylcholinesterase and enhances the intrinsic action of acetylcholine on nicotinic receptors.

The cognitive dysfunction (memory, attention, learning) in dementia of the Alzheimer type is related to the profound dysfunction of the cholinergic neurotransmission system in the brain. Galantamine, a tertiary alkaloid, enhances the efficacy of the physiologically available acetylcholine through a dual mechanism of action: acetylcholinesterase inhibition and nicotinic receptor modulation.

Pharmacodynamic effects

Galantamine is a selective, competitive and reversible inhibitor of acetylcholinesterase, the enzyme responsible for the breakdown of the neurotransmitter acetylcholine. As a consequence, the breakdown of acetylcholine, released by the remaining healthy brain cells, is slowed down leaving more neurotransmitter available to support normal brain function.

In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. Stimulation of nicotinic receptors has been associated with improved cognitive function and neuroprotection against amyloid induced neurotoxicity. Amyloid peptide is the major component of amyloid plaques, one of the hallmarks of Alzheimer's disease. Modulation of the nicotinic receptor could also lead to enhanced neurotransmitter release, including the release of acetylcholine.

Animal studies have shown that galantamine effectively increases brain acetylcholine levels and enhances cognitive function, as inferred from its pharmacological mode of action.

Clinical efficacy and safety

At the time of registration, more than 2500 patients in Australia, Canada, Europe and USA had received galantamine in both controlled and uncontrolled clinical studies. The efficacy of REMINYL in treating patients with the symptoms of mild to moderate Alzheimer's disease was assessed in three pivotal double blind, randomised, placebo controlled clinical trials of 5 months (GAL-USA-10) and 6 months duration (GAL-INT-1 and GAL-USA-1). GAL-INT-1 and GAL-USA-1 studied the effect of galantamine at maintenance doses of 24 mg/day (n=428) and 32 mg/day (n=429). GAL-USA-10 (n=979) was conducted to evaluate the efficacy and tolerability of lower maintenance doses (16 mg/day and 24 mg/day) of galantamine with a slower dose escalation regimen. REMINYL was shown to be effective at 16, 24 and 32 mg/day in controlled clinical trials.

In the assessment of galantamine for the treatment of Alzheimer's disease, improvement of symptoms was assessed in three domains: cognition as measured by objective tests, activities of daily living and an overall clinical response as measured by a global assessment. All three domains were assessed in each of the above pivotal clinical trials. In addition, a fourth domain of behavioural assessment was included in GAL-USA-10 and GAL-INT-2.

NINCDS-ADRDA criteria were used to select patients with probable Alzheimer's disease. Mild to moderate disease was defined as Mini Mental State Exam score of 11-24 with an ADAScog score $\geq$12 at baseline. Other causes of dementia were excluded, and patients with psychiatric illness were excluded based on DSM-IV criteria.

Cognitive Endpoint – ADAScog

The cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAScog) was used to measure the ability of REMINYL to improve cognitive performance. The ADAScog is an established scale, specifically designed to assess cognitive therapy in Alzheimer's disease. The ADAScog is a multi-item test battery that examines select aspects of cognitive performance including memory, orientation, attention, reasoning, language and praxis. The ADAScog scale extends from 0 to 70, higher scores indicating greater cognitive impairment. Elderly, normal patients may score as low as 0 or 1 unit,

but individuals judged not to be demented can score higher. The mean score of patients entering each study was approximately 27 units. The ADAScog score is reported to deteriorate at a rate of about 8 to 11 units per year for untreated patients with Alzheimer's disease.

As shown in Figure 1, the cognitive performance of patients, who were treated with REMINYL in GAL-INT-1 and GAL-USA-1, was statistically significantly better than that of patients who were given placebo ($p<0.001$). The cognitive improvement was also statistically significant from as early as 3 weeks after the start of treatment.

The cognitive performance of patients treated with REMINYL, at the end of the 6 month observation period, was still well above the baseline performance whereas patients treated with placebo deteriorated. The effect size compared to placebo increased over time and was greatest at the end of the double-blind treatment period. Sub-analysis revealed that patients treated with REMINYL performed better than placebo treated patients in all clusters addressing specific cognitive domains contained in the ADAScog. This shows that the overall effect of treatment was not related to a specific domain of cognitive performance, but that REMINYL improved all domains.

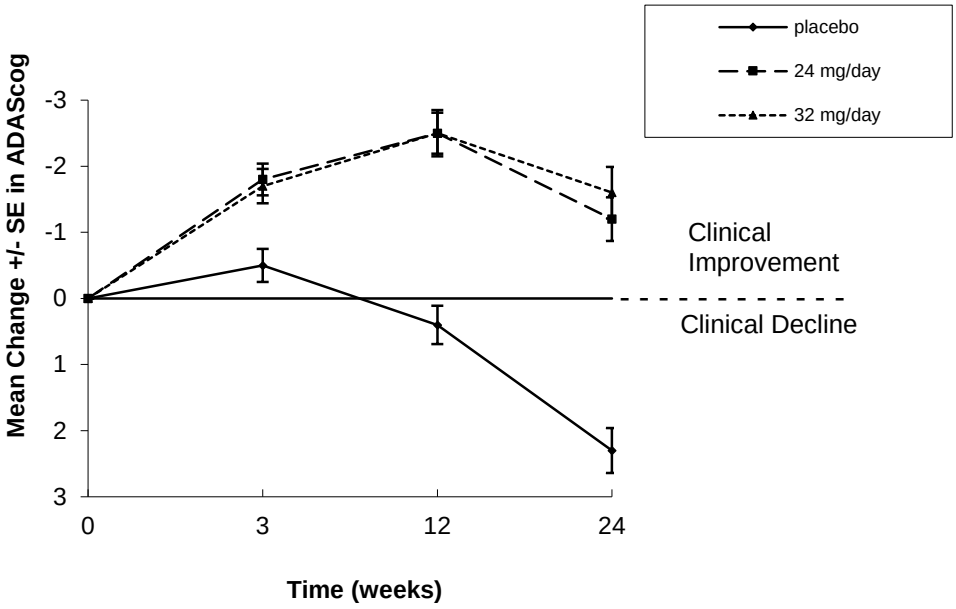

Figure 1. Mean (±SE) change from baseline in ADAScog score over time (GAL-INT-1, GAL-USA-1)

Treatment effect was present in all patient subgroups and the most pronounced effects were seen in patients in the more advanced stages of disease. There were no significant treatment-by-subgroup interactions for sub-populations of age, gender, race, baseline weight, APO-E genotype and smoking status. Statistically significant findings were consistent between trials and countries, and robust with respect to possible selective censoring due to premature discontinuation or missing data.

In GAL-USA-10, statistically significant reductions in cognitive impairment was observed for the 16 and 24 mg/day groups ($p<0.001$) when compared to placebo after 5 months. The results for the 16 and 24 mg/day doses were similar at all time points (see Figure 2).

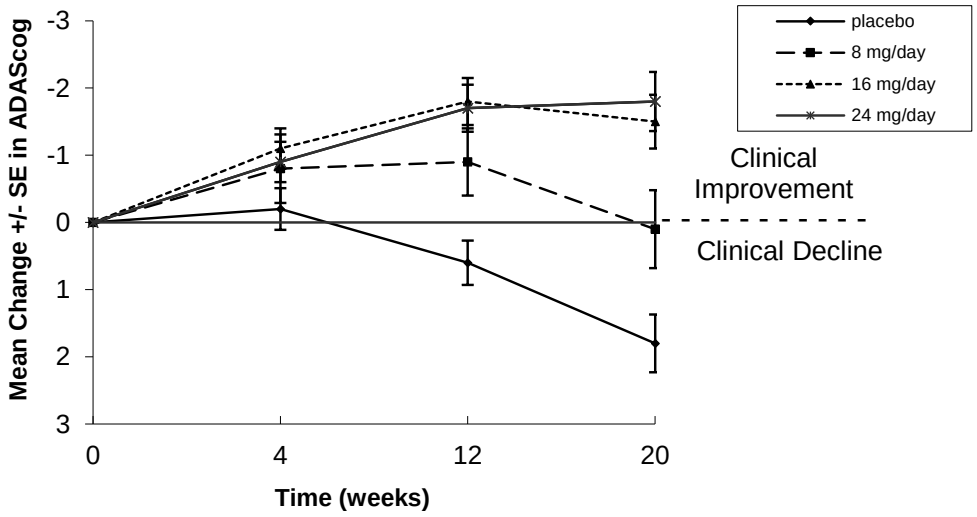

Figure 2. Mean changes ± SE from baseline in ADAScog/11 score over time (GAL-USA-10)

Global Endpoint – CIBICplus

The Clinician Interview Based Impression of Change with carer input (CIBICplus) was used to provide global clinical assessment. CIBICplus involves an independent, semi-structured medical interview assessing all domains of cognition and activities of daily living. By its nature the CIBICplus is a crude and insensitive outcome measure, less responsive to drug effects than psychometric tests alone. It was intentionally designed so that any statistically significant difference between two groups is evidence of a clinically relevant effect.

Figure 3 displays the percentage of patients who improved or did not deteriorate over the course of the trial according to CIBICplus. In both trials there were always more patients treated with REMINYL found to have improved or not deteriorated compared to the placebo-treated patients, and the differences were consistently statistically significant.

The results of the CIBICplus indicate that independent clinicians were able to discern a treatment effect and thus the result on the global test confirm the findings on the ADAScog and render it clinically relevant.

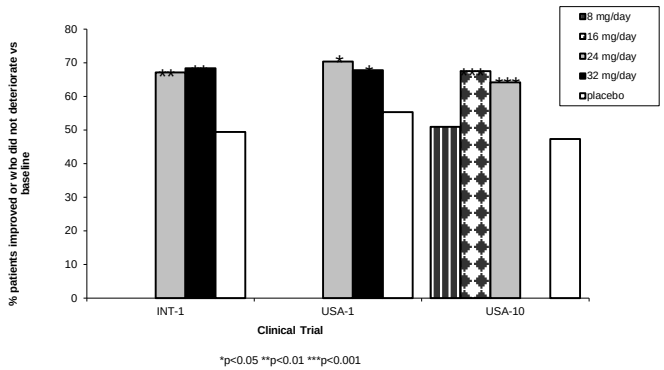

Figure 3. CIBICplus. Percentage of patients improved or who did not deteriorate vs baseline at end of trial (Observed Case Analysis)

Functional Endpoint - DAD

The Disability Assessment in Dementia (DAD) was used to assess three categories of activities of daily living (ADL): the basic ADL's comprise dressing, hygiene, continence and eating; the instrumental ADL's consist of meal preparation, telephoning, housework, taking care of finance and correspondence and the ability to safely stay at home. The third category consists of one topic - leisure activities. The specific merit of the DAD is that it provides the possibility to assess different levels of performance: initiation, planning and organisation, and effective performance of the activity. The maximum score on the DAD is 46 and higher scores indicate less disability. This scale often fails to show improvements in activities of daily living, since once a patient loses the ability to perform a certain task, carers often remove the possibility for the patient to perform that activity again. Hence the test is not sensitive to improvements in function. However, maintaining function in a progressive disease can be considered a positive outcome that the scale is likely to document.

As expected, the functional endpoint (DAD) showed more variability within groups and showed less consistent treatment effects compared to the cognitive and global endpoints. In all trials patients treated with REMINYL maintained functionality over the observation period. Significant differences between placebo and REMINYL were seen in trials where a significant placebo deterioration was present.

In GAL-USA-10, ADCS/ADL (Alzheimer's Disease Cooperative Study Activities Daily Living) inventory was used to measure the overall change in activities of daily living. At months 3 and 5, a significantly superior treatment effect was demonstrated in the groups receiving 16 and 24 mg/day of galantamine when compared to the placebo group.

The effect of REMINYL on caregiver burden was evaluated in clinical studies. In GAL-INT-1, the average time required for patient's care was less in the REMINYL group as opposed to the placebo group at month 6. Patients treated with REMINYL could also be left unsupervised for a longer period of time than the placebo group.

Clinically Relevant Response – Overall Benefit

Figure 4 shows the results of a pooled analysis of the two pivotal studies in which different types of "responders" are assessed. A clinically relevant response was categorised either as:

- no decline on ADAScog,
- improvement of at least 4 points on the ADAScog,
- improvement on the CIBICplus, or
- improvement of at least 4 points on the ADAScog and no worsening on the CIBICplus and no worsening on the DAD.

There is a statistically significant difference for both doses of galantamine compared to placebo for all response categories.

In order to assess the overall efficacy of REMINYL in the treatment of the symptoms of mild to moderate Alzheimer's disease, all three endpoints (cognitive, global and functional performance) must be considered to determine whether a clinically significant effect can be concluded.

Figure 4 shows the percentage of patients with a clinically significant response on a combination of scales: improvement of at least 4 points on the ADAScog and no worsening on the CIBICplus and no worsening on the DAD. In the placebo, group 5.5% of patients met the criterion whilst this percentage was 14.3% for patients treated with REMINYL 24 mg daily and 13.3% for patients treated with REMINYL 32 mg daily. The difference between placebo and both REMINYL treatment groups was statistically significant (p<0.001).

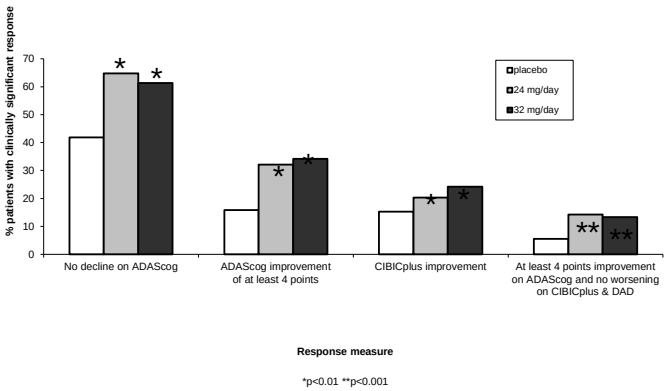

Figure 4. Percentage of patients with clinically significant response vs placebo (Observed Case Analysis) (GAL-INT-1 & GAL-USA-1)

Behavioural Endpoint – NPI (Neuropsychiatric Inventory)

NPI was used as an additional outcome measure to evaluate behavioural disturbances in GAL-USA-10. The NPI covered 10 domains of behaviours seen in patients with Alzheimer's disease, which included delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition irritability/lability and aberrant motor behaviour. Caregivers were also given the opportunity to rate the amount of distress each behaviour caused them (the caregivers).

In comparison to the placebo group or the 8 mg/day group, galantamine showed a statistically significant ($p \leq 0.05$) advantage in maintaining the total NPI score after 5 months of treatment at doses of 16 mg/day and 24 mg/day. Stabilised behaviour was observed in patients receiving 16 or 24 mg/day of galantamine.

Long term safety and efficacy

The long term safety and efficacy of 24 mg REMINYL (12 mg twice daily) in Alzheimer's disease patients who had completed GAL-USA-1 was evaluated during an additional six month open label extension. These patients had received either placebo, 24 mg or 32 mg of galantamine during the initial six month trial.

The extension study (GAL-USA-3) results support the findings of the 24 week pivotal trials in demonstrating the safety and efficacy of REMINYL. Patients treated with REMINYL 24 mg/day for the entire 12 month period maintained cognitive benefits during the second six months of treatment. They finished the extension trial with ADAScog scores no worse than they were at baseline. Although no placebo group was available for comparison in this study, the result is quite significant considering that literature suggests the average decline for Alzheimer's disease patients on the ADAScog over 12 months is eight to eleven points.

Patients who received placebo for the first 24 week period in GAL-USA-1 and were then given REMINYL 24 mg daily in GAL-USA-3, did experience an improvement in their cognitive function according to ADAScog after 3 months treatment with REMINYL. Although the ADAScog score at the end of the initial placebo phase had deteriorated by 2.2 points from baseline (ie at the start of GAL-USA-1), there was no further statistically significant change for this group during treatment with REMINYL.

No rebound effect on cognitive performance was seen in patients abruptly withdrawn from REMINYL treatment. Contrary to what would be expected from a purely symptomatic treatment, patients did not completely lose the treatment benefits during a six-week observation period after cessation of REMINYL treatment.

Gastrointestinal tolerability of REMINYL improved during modified dosing, and no unexpected time-dependant adverse events were apparent.

REMINYL modified release capsules

The efficacy of REMINYL modified release (PR) capsules was studied in a randomized, double-blind, placebo and active-controlled trial using a 4-week dose escalation, flexible dosing regimen of 16 or 24 mg/day for a treatment duration of 6 months. The three treatment groups in the study were REMINYL modified release capsule, REMINYL immediate release tablets and placebo.

The subject inclusion entry MMSE criterion in this study was 10 to 24.

In the protocol-specified primary efficacy analysis for the two endpoints (ADAS-cog/11 and CIBIC-plus), at month 6, REMINYL PR capsules showed a statistically significant improvement over placebo for ADAS-cog/11. A numerical trend in favour of REMINYL modified release capsules was observed for the CIBIC-plus score, however neither REMINYL PR capsules nor REMINYL IR tablets achieved the nominal statistical significance when compared to placebo. This may have been due to the overrepresentation of subjects with a screening MMSE score >22 in the placebo group. These patients contributed to the disproportionately high placebo response rate. In addition, REMINYL PR capsules 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 modified release capsules and REMINYL tablets, which served as an active control in this study.

5.2 PHARMACOKINETIC PROPERTIES

Galantamine is a low clearance drug (plasma clearance of approximately 300 mL/min) with a moderate volume of distribution (average Vd_{ss} of 175 L). The disposition of galantamine is bi-exponential, with a terminal half-life in the order of 7-8 hours.

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

Absorption

The absorption of REMINYL modified release capsules is rapid. The absolute bioavailability of galantamine is high, 88.5 ± 5.4%. The presence of food delays the rate of absorption (t_{max}) and reduces peak concentration (Cmax) by about 25%, without affecting the extent of absorption (AUC).

The C_{max} value is reached after 4.4 hours. Food has no effect on AUC and C_{max} of the modified release capsules and slightly increases t_{max} by about 12%.

The mean pharmacokinetic parameters in 22 healthy adults following the 24 mg modified release capsules are summarized in Table 4.

Table 4. Mean + SD Pharmacokinetic Parameters

Parameters	Modified release capsule Fed (n = 22)	Modified release capsule Fasted (n = 22)
AUC_{24h}, ng.h/mL	1015 + 214	968 + 193
$C_{max, ng/mL}$	70.6 + 15.0	63.0 + 12.0
$C_{min, ng/mL}$	19.9 +7.2	18.8+ 4.6
$T_{max, h}$	4.9+ 1.7	4.4 + 1.7
$T_{1/2, h}$	8.0 + 2.0 (n = 8)	8.3 + 1.2 (n = 7)

Distribution

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%), whereas the fraction of galantamine bound to plasma proteins in only 8.4%. The blood to plasma concentration ratio of galantamine is 1.17.

Biotransformation

Major metabolic pathways were N-oxidation, N-demethylation, O-demethylation, glucuronidation and epimerisation. O-demethylation was far more important in extensive metabolisers of CYP2D6. The levels of excretion of total radioactivity in urine and faeces did not differ between poor and extensive metabolisers. *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 metabolisers, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In plasma from extensive metabolisers, the glucuronide of O-desmethylgalantamine was also present.

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

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 faeces. After intravenous 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.

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 between 52-104 mL/min) or 67% in severe renal impairment (creatinine clearance between 9-51 mL/min), compared to age and weight-matched healthy subjects (creatinine clearance greater than or equal to 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.

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%.

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

Linearity

Galantamine pharmacokinetics of REMINYL modified release capsules are dose proportional within the studied dose range of 8 mg to 24 mg in elderly and young age groups. No difference in the pharmacokinetics of REMINYL modified release capsules were noted following single and repeated once daily dosing indicating no significant drug accumulation. The AUC and terminal half-life following the repeated dosing are similar to those following the single dose of galantamine.

5.3 PRECLINICAL SAFETY DATA

Galantamine showed no drug-related increases in tumour incidences in transgenic tumour-suppressor-gene p53-deficient mice at plasma $AUC_{0\text{-}24h}$ levels slightly greater than those in humans after the maximum recommended dose. There was also no increase in tumour incidences in a 24-month carcinogenicity study in Charles River CD1 mice at plasma $AUC_{0\text{-}24h}$ levels 1 to 2 times those in humans at the maximum recommended dose.

In a 24-month carcinogenicity study in Wistar rats, dose-related increases in the incidences of endometrial (adeno) carcinomas and sarcomas of the genital tract were observed in females. At the no-effect level of 2.5 mg/kg/day, systemic exposure (plasma $AUC_{0\text{-}24h}$) was slightly greater than that in humans at the maximum therapeutic dose. The mechanism of tumour development has not been clearly established but may be related to decreased prolactin levels.

Galantamine was not mutagenic in bacterial reverse mutation tests in *Salmonella typhimurium* and *Escherichia coli* or in a mammalian gene mutation test *in vitro*. Galantamine did not induce chromosome aberrations in Chinese hamster ovary cells in vitro or in the micronucleus test in mice *in vivo*.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

REMINYL contains the following inactive ingredients:

Capsule pellets:
Diethyl phthalate
Ethylcellulose
Hypromellose
Macrogol
Sugar spheres (containing sucrose and maize starch)
Opadry clear OY-7240 (containing hypromellose and macrogol 400)

Capsule body:
Gelatin
Titanium dioxide
Iron oxide red (16 mg and 24 mg capsule)
Iron oxide yellow (24 mg capsule)

Printing ink:
Opacode black S-1-277002 or TekPrint SW-9008 Black Ink (both inks contain shellac, iron oxide black and propylene glycol)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

8mg Modified release capsules:
PVC-PE-PVDC/Al Blisters in pack size of 7 or 28
HDPE Bottles in pack size of 30 or 300

16mg Modified release capsules:
PVC-PE-PVDC/Al Blisters in pack size of 28, 56 or 84
HDPE Bottles in pack size of 30 or 300

24mg Modified release capsules:
PVC-PE-PVDC/Al Blisters in pack size of 28, 56 or 84
HDPE Bottles in pack size of 30 or 300

Not all pack types and pack sizes are marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

23 December 2004

10. DATE OF REVISION OF THE TEXT

03 August 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Update to the dose form to ‘modified release capsules’.