AUSTRALIAN PRODUCT INFORMATION

GALANTYL®

(Galantamine) modified release capsules

1 NAME OF THE MEDICINE

Galantamine (as hydrobromide)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 8 mg; 16 mg; or 24 mg of galantamine (as hydrobromide) as the active ingredient.

Excipients with known effect: traces of sulfites

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

GALANTYL 8 mg modified release capsules are size 2, hard gelatin capsules with a white body and pink cap printed in black ink "MYLAN" over "GT 8" on both the body and the cap.

GALANTYL 16 mg modified release capsules are size 2, hard gelatin capsule with a white body and pale pink cap printed in black ink "MYLAN" over "GT 16" on both the body and the cap.

GALANTYL 24 mg modified release capsules are Size 1, hard gelatin capsule with a white body and pink cap printed in black ink "MYLAN" over "GT 24" on both the body and the cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

GALANTYL modified release capsules should be administered once daily in the morning, preferably with food. Ensure adequate fluid intake during treatment. The dose of GALANTYL 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 galantamine.

Concomitant Treatment

In patients co-treated with ketoconazole or potent inhibitors of cytochrome P450 2D6, dose reductions can be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in Patients with Hepatic and Renal 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, 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 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 galantamine is contraindicated (see Section 4.3 CONTRAINDICATIONS).

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 galantamine is contraindicated (see Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

Galantamine is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or any excipients used in the formulation (see Section 6.1 LIST OF EXCIPIENTS).

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with Caution in the Following Circumstances

As with other cholinomimetics, galantamine 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 (e.g. digoxin and beta blockers) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 (e.g. hyperkalaemia, hypokalaemia) or congestive cardiac failure, especially NYHA group III-IV. In clinical trials, use of galantamine has been associated with syncope and rarely with severe bradycardia.

There have been reports of QT prolongation in patients using therapeutic doses of galantamine and of torsades de pointes in association with overdose. Galantamine should therefore be used with caution in patients with prolongation of the QT interval, in patients treated with drugs affecting the QT interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances (see also 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 galantamine showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. The use of galantamine is not recommended in patients with gastrointestinal obstruction or recovering from gastrointestinal surgery.

Neurological Conditions:

Cholinomimetics are believed to have some potential to cause seizures. Convulsions have been reported with galantamine (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Seizure activity may also be a manifestation of Alzheimer's disease. In rare cases an increase in cholinergic tone may worsen Parkinsonian symptoms and symptoms related to extrapyramidal disorders (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) Post-marketing 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. Similarly, caution should be exercised in treating patients with active pneumonia.

Genitourinary:

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

Use in Other Types of Dementia

The benefit of galantamine in patients with other types of dementia or other types of memory impairment has not been demonstrated. Galantamine 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 generalised exanthematous pustulosis) have been reported in patients receiving galantamine (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). It is recommended that patients be informed about the signs of serious skin reactions, and that use of galantamine 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.

Mortality in Subjects with Mild Cognitive Impairment

Galantamine 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.

In two randomised placebo-controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI), a total of 14 deaths were initially recorded in the double-blind period with 13 subjects randomised to galantamine (n=1026) and 1 randomised to placebo (n=1022). The relative risk (95% exact confidence interval) was 6.19 (2.17, 17.68). This dataset consists of the number of deaths originally recorded in the double-blind period of the 2 studies and up to 30 days after stopping study medicine. The deaths were due to various causes which could be expected in an elderly population; about half of the galantamine and placebo deaths appeared to result from various vascular causes (myocardial infarction, stroke and sudden death).

Although the difference in initially recorded mortality between galantamine and placebo-treated groups was significant, the results were highly discrepant with other studies of galantamine. Specifically, in these two MCI studies, the initially recorded mortality rate in subjects randomised to placebo was markedly lower than the rate in placebo-treated patients in trials of galantamine in Alzheimer's disease or other dementias (0.7 per 1000 person years compared to 22-61 per 1000 person years, respectively). Although the initially recorded mortality rate in MCI subjects randomised to galantamine was also lower than that observed in galantamine - treated patients in Alzheimer's disease and other dementia trials (10.2 per 1000 person years compared to 23-31 per 1000 person years, respectively), the relative difference was much less. 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 galantamine group. Furthermore, in the MCI studies, no subjects in the placebo group died after 6 months, a highly unexpected finding in this population. 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. Mortality status and cause of death where known were collected for subjects who had dropped out of the two studies and hence were not recorded in the initial analysis. Three additional deaths were identified as specified in the protocol; thus 14 deaths in subjects randomised to galantamine and 3 in placebo occurred during the double-blind period within up to 30 days of stopping study medicine. The relative risk (95% exact confidence interval) was 4.08 (1.57, 10.57). Information on subsequent treatment or adverse events following drop out was not collected and therefore the data may be subjected to bias. 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 galantamine. The relative risk (95% exact confidence interval) was 1.24 (0.84, 1.83).

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

Use in 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 DOSE AND METHOD OF ADMINISTRATION).

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

Use in 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 galantamine is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Use in the Elderly

No data available.

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic interactions

Because of its mechanism of action, galantamine should not be given concomitantly with other cholinomimetics. Galantamine antagonises the effect of anticholinergic medication. As expected with

cholinomimetics, a pharmacodynamic interaction is possible with medicines that significantly reduce the heart rate (e.g. digoxin and beta blockers). Caution should be taken with medicinal products that have potential to cause torsades de pointes. In such cases an ECG should be considered (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Galantamine, as a cholinomimetic, is also likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Pharmacokinetic 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 medicine 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 (e.g. quinidine, paroxetine, fluoxetine or fluvoxamine) or CYP3A4 (e.g. ketoconazole), patients may experience an increase 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-aspartate (NMDA) receptor antagonist, at a dose of 10 mg once daily for 2 days followed by 10 mg twice daily for 12 days had no effect on the pharmacokinetics of galantamine 16 mg once daily at steady state.

Effect of Galantamine on the Metabolism of other Medicines

Therapeutic dose of galantamine (12 mg twice daily) had no effect on the kinetics of digoxin and warfarin. Galantamine did not affect the increase 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

Effects on 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.

Use in Pregnancy

Pregnancy Category: B1

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

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

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.

Use in Lactation

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

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. Galantamine 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Double-Blind Data – Adverse Drug Reactions Reported at ≥1% Frequency

The safety of galantamine 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 Drug Reactions (ADRs) reported by ≥1% of galantamine - treated subjects in these trials are shown in Table 1.

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

System/Organ Class Adverse Reaction	**Galantamine (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
Diarrhoea	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 randomised, double-blind, placebo-controlled clinical trial, the safety profile of once-daily treatment with galantamine modified release capsules was similar in frequency and nature to that seen with tablets.

Nausea and vomiting, the most frequent adverse drug reactions, occurred mainly during titration periods, lasted less than a week in most cases and the majority of patients had one episode. Prescription of antiemetics 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 galantamine 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 drug reactions (ADRs) not reported in Table 1 that occurred in <1% of galantamine-treated subjects in the double-blind and 5 open-label clinical datasets are listed in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of Galantamine - 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

Post-marketing data

In addition to the adverse drug reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing 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 Post-marketing Experience with Galantamine

	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
Nightmare	Not known	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-Jonson Syndrome	Very rare	Not known
Acute generalised exanthematous pustulosis	Very rare	Not known
Erythema multiforme	Very rare	Not known
Investigations		
Hepatic enzyme increased	Very rare	Uncommon

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 Torsades 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 (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 hospitalisations 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 hospitalisation. 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 given intravenously is recommended, with subsequent doses based on the clinical response.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Galantamine is a cholinomimetic with a dual mechanism of action. Galantamine is a reversible inhibitor of the enzyme acetylcholinesterase, and enhances the intrinsic action of acetylcholine on nicotinic receptors.

Pharmacodynamics

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.

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 Trials

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 galantamine 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. Galantamine 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 ≥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 galantamine 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.

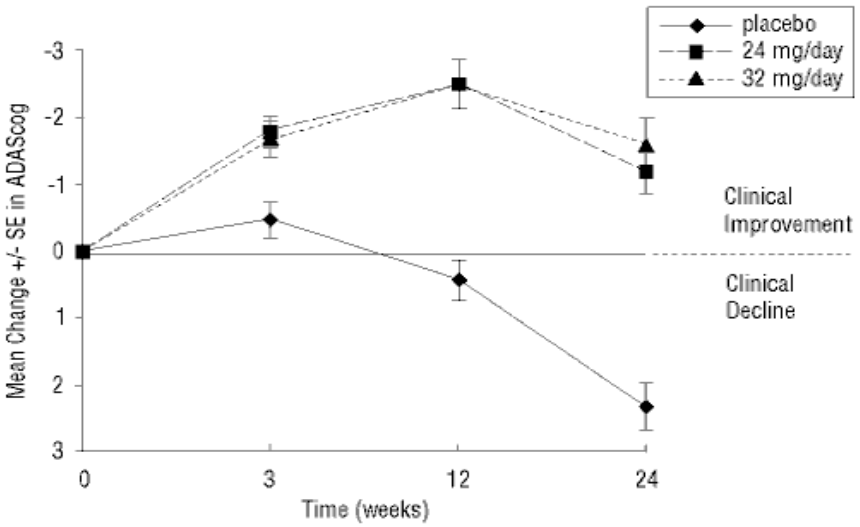
As shown in Figure 1, the cognitive performance of patients, who were treated with galantamine in GAL-INT-1 and GAL-USA-1, was statistically significantly better than that of patients who were given placebo

($p<0.001$). 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 galantamine, 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 galantamine 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 galantamine improved all domains.

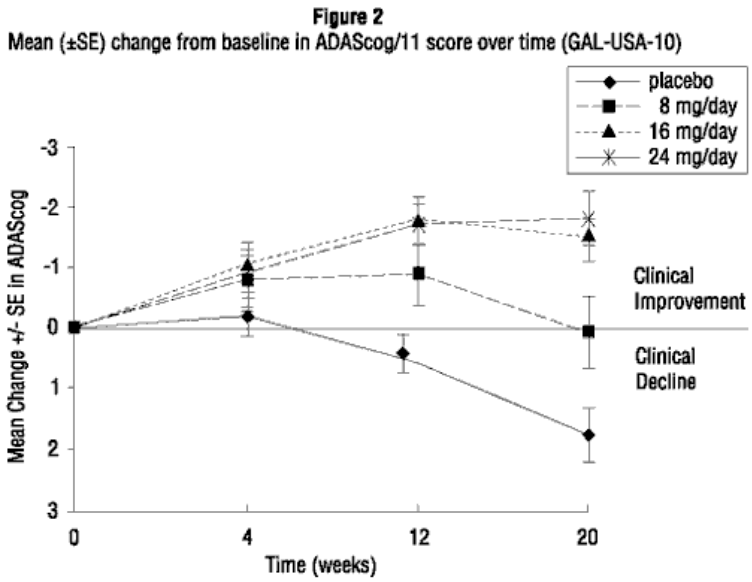
Figure 1

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 of 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).



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 medicine 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 galantamine 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.

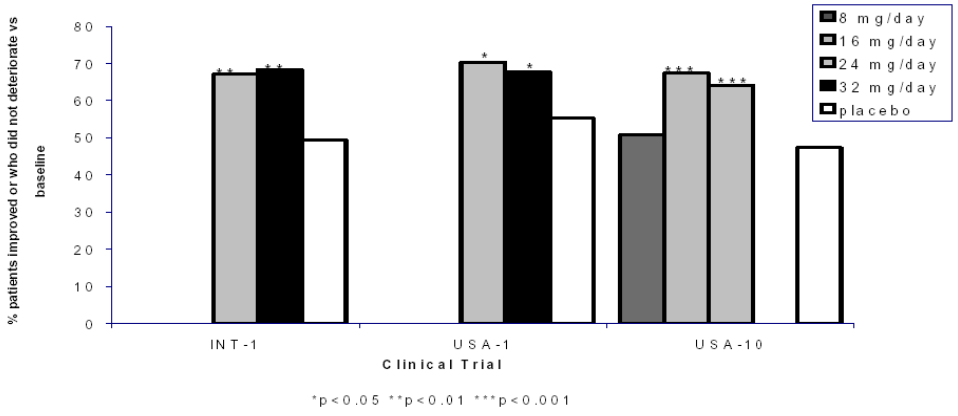


Figure 3. CIBICplus. Percentage of patients improved or who did not deteriorate vs baseline at end of trial (Observed Case Analysis)

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 galantamine maintained functionality over the observation period. Significant differences between placebo and galantamine 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 galantamine on caregiver burden was evaluated in clinical studies. In GAL-INT-1, the average time required for patients care was less in the galantamine group as opposed to the placebo group at month 6. Patients treated with galantamine 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.

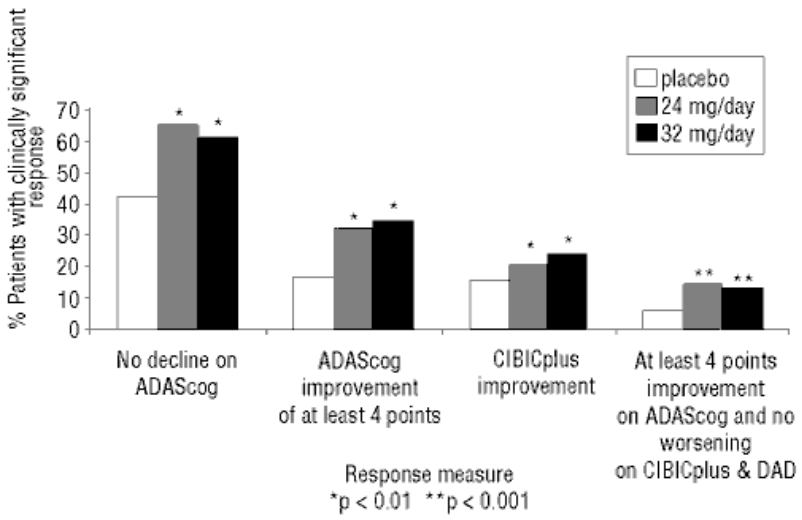
There is a statistically significant difference for both doses of galantamine compared to placebo for all response categories.

In order to assess the overall efficacy of galantamine 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 galantamine 24 mg daily, and 13.3% for patients treated with galantamine 32 mg daily. The difference between placebo and both galantamine 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 (Neuropsychiatry 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 galantamine (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 galantamine. Patients treated with galantamine 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 than given galantamine 24 mg daily in GAL-USA-3, did experience an improvement in their cognitive function according to ADAScog after 3 months treatment with galantamine. Although the ADAScog score at the end of the initial placebo phase had deteriorated by 2.2 points from baseline (i.e. at the start of GAL-USA-1), there was no further statistically significant change for this group during treatment with galantamine.

No rebound effect on cognitive performance was seen in patients abruptly withdrawn from galantamine 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 galantamine treatment.

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

Galantamine (as hydrobromide) modified release capsules

The efficacy of galantamine modified release capsules was studied in a randomised, 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 galantamine modified release capsule, galantamine immediate release (IR) tablets and placebo.

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 10 to 24 with an ADAScog/11 score ≥18 at screening.

In the protocol-specified primary efficacy analysis for the two endpoints (ADAS-cog/11 and CIBIC-plus), at month 6, galantamine ER capsules showed a statistically significant improvement over placebo for ADAS-cog/11. A numerical trend in favour of galantamine ER capsules was observed for the CIBIC-plus score, however neither galantamine ER capsules or galantamine 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, galantamine ER capsules was statistically significantly better than placebo in improving activities of daily living (ADCS-ADL), a key secondary efficacy measure. There were no clinically relevant differences in medicine compliance, including dose titration, dose reduction, discontinuation, and daily dose compliance.

Efficacy results were similar for galantamine ER capsules and galantamine tablets, which served as an active control in this study.

5.2 PHARMACOKINETIC PROPERTIES

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

After repeated oral dosing of the immediate release tablets (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 for the immediate release formulation.

Galantamine modified release capsules (24 mg once daily) are bioequivalent to the immediate release (IR) tablets (12 mg twice daily) with respect to AUC_{24h} and C_{min} at steady state. The C_{max} value was about 24% lower than that of tablet. Galantamine pharmacokinetics of galantamine ER capsules are dose proportional within the studied dose range of 8 mg to 24 mg in elderly and young age groups. The terminal half-life of galantamine ER capsules is similar to that of immediate release tablet.

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

Absorption

Immediate-release tablets: Absorption is rapid, with a T_{max} of about 1 hour. 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 (C_{max}) by about 25%, without affecting the extent of absorption (AUC).

Modified release capsules: well absorbed with T_{max} value around 4.4 hours. Food has no significant effect on AUC of the modified release capsules. C_{max} was increased by about 12% and T_{max} increased by about 30 minutes when the capsule was given after food. However, these changes are unlikely to be clinically significant.

The mean pharmacokinetic parameters at steady state in 22 healthy adults following the 24 mg once daily modified release capsules and the 12 mg twice daily immediate release tablets are summarised in Table 4.

Table 4. Mean + SD Pharmacokinetic Parameters

Parameters	Modified release capsule Fed (n = 22)	Modified release capsule Fasted (n = 22)	Immediate release tablet Fasted (n = 22)
AUC_{24h}, ng.h/mL	1015 ± 214	968 ± 193	1050 ± 239
C_{max}, ng/mL	70.6 ± 15.0	63.0 ± 12.0	84.3 ± 21.4
C_{min}, ng/mL	19.9 ± 7.2	18.8 ± 4.6	21.7 ± 7.9
T_{max}, h	4.9 ± 1.7	4.4 ± 1.7	1.2 ± 0.6
$T_{1/2}$, h	8.0 ± 2.0 (n = 8)	8.3 ± 1.2 (n = 7)	8.5 ± 1.3 (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 is 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 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.

Excretion

Seven days after a single oral dose of 4 mg ^{3}H-galantamine (solution), 90-97% of the radioactivity was recovered in urine and 2.2-6.3% in the faeces. After intravenous and oral solution 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 (8 mg immediate release tablet) 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 (4 mg immediate release tablet) were increased by about 30%.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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*.

Carcinogenicity

Galantamine showed no medicine-related increase 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Empty Gelatin Capsule RM 991 Size 2 White op body - Pink op cap with Mylan and GT8 in Black Ink (ID 105899 – 8 mg)

Empty Gelatin Capsule RM 992 Size 2 White op body - Pink op cap with Mylan and GT16 in Black Ink (ID 105900 - 16 mg)

Empty Gelatin Capsule RM 993 Size 1 White op body - Pink op cap with Mylan and GT24 in Black Ink (ID 105898 – 24 mg)

Kollidon Sr (ID 106078), povidone, hydrogenated vegetable oil, and magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al blister packs.

Pack sizes: All strengths of GALANTYL modified release capsules are available packs of 28 and 30.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 157934 – GALANTYL galantamine (as hydrobromide) 8 mg modified release capsule blister pack

AUST R 157932 – GALANTYL galantamine (as hydrobromide) 16 mg modified release capsule blister pack

AUST R 157933 – GALANTYL galantamine (as hydrobromide) 24 mg modified release capsule blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

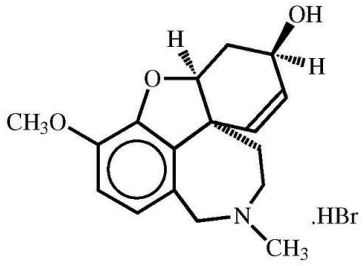
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : (4a*S*, 6*R*, 8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2] benzazepin-6-ol hydrobromide

Structural formula :



Molecular formula : $C_{17}H_{21}NO_3.HBr$ Molecular weight : 368.27

Galantamine hydrobromide, is a white to almost white powder with a solubility in water of 3.1 g/100 mL. Galantamine hydrobromide contains three chiral centres and is presented as a single enantiomer.

CAS Number

1953-04-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

23/04/2010

10 DATE OF REVISION

19/11/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.8	Update to Adverse Reactions related to psychiatric disorders and the addition of post-marketing adverse reaction “Nightmare”.

GALANTYL® is a Viatris company trade mark

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