

Galantamine

Core Safety Profile

4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Adults/Elderly

Administration

Prolonged Release capsules only

Galantamine prolonged-release capsules should be administered once daily in the morning, preferably with food. The capsules should be swallowed whole together with some liquid. The capsules must not be chewed or crushed.

Immediate Release Tablets/oral solution

Galantamine immediate release tablets/oral solution should be administered twice a day, preferably with morning and evening meals

Ensure adequate fluid intake during treatment (see section 4.8).

Before start of treatment

The diagnosis of probable Alzheimer type of dementia should be adequately confirmed according to current clinical guidelines (see section 4.4).

Starting dose

Prolonged Release capsules only

The recommended starting dose is 8 mg/day for 4 weeks.

Immediate Release Tablets/oral solution

The recommended starting dose is 8 mg/day (4 mg twice a day) for four weeks.

Maintenance dose

- The tolerance and dosing of galantamine should be reassessed on a regular basis, preferably within three months after start of treatment. Thereafter, the clinical benefit of galantamine and the patient's tolerance of treatment should be reassessed on a regular basis according to current clinical guidelines. Maintenance treatment can be continued for as long as therapeutic benefit is favourable and the patient tolerates treatment with

galantamine. Discontinuation of galantamine should be considered when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment.

Prolonged Release capsules only

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

Immediate Release Tablets/oral solution

- The initial maintenance dose is 16 mg/day (8 mg twice a day) and patients should be maintained on 16 mg/day for at least 4 weeks.

Prolonged Release capsules/oral solution

- An increase to the maintenance dose of 24 mg/day should be considered on an individual basis after appropriate assessment including evaluation of clinical benefit and tolerability.

Immediate Release Tablets

- An increase to the maintenance dose of 24 mg/day (12 mg twice a day) should be considered on an individual basis after appropriate assessment including evaluation of clinical benefit and tolerability.
- In individual patients not showing an increased response or not tolerating 24 mg/day, a dose reduction to 16 mg/day should be considered.
- There is no rebound effect after abrupt discontinuation of treatment (e.g. in preparation for surgery).

Prolonged Release capsules only

Switching to Galantamine prolonged-release capsules from Galantamine tablets or Galantamine oral solution

It is recommended that the same total daily dose of galantamine is administered to patients. Patients switching to the once-daily regimen should take their last dose of galantamine tablets or oral solution in the evening and start galantamine prolonged-release capsules once daily the following morning.

Paediatric population

There is no relevant use of galantamine in the paediatric population.

Hepatic and renal impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic or renal impairment.

Prolonged Release capsules only

In patients with moderately impaired hepatic function, based on pharmacokinetic modelling, it is recommended that dosing should begin with 8 mg prolonged-release capsule once every other day, preferably taken in the morning, for one week. Thereafter, patients should proceed with 8 mg once daily for four weeks. In these patients, daily doses should not exceed 16 mg.

Immediate Release Tablets/oral solution

In patients with moderately impaired hepatic function, based on pharmacokinetic modelling, it is recommended that dosing should begin with 4 mg once daily, preferably taken in the morning, for at least one week. Thereafter, patients should proceed with 4 mg twice daily for at least 4 weeks. In these patients, daily doses should not exceed 8 mg twice daily.

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

Concomitant treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Since no data are available on the use of galantamine in patients with severe hepatic (Child-Pugh score greater than 9) and severe renal (creatinine clearance less than 9 ml/min) impairment, galantamine is contraindicated in these populations. Galantamine is contra-indicated in patients who have both significant renal and hepatic dysfunction.

4.4 Special warning and precautions for use

Galantamine is indicated for a patient with mild to moderately severe dementia of the Alzheimer type. The benefit of galantamine in patients with other types of dementia or other types of memory impairment has not been demonstrated. In 2 clinical trials of two years duration in individuals with so called mild cognitive impairment (milder types of memory impairment not fulfilling the criteria of Alzheimer dementia), galantamine therapy failed to demonstrate any benefit either in slowing cognitive decline or reducing the clinical conversion to dementia. The mortality rate in the galantamine group was significantly higher than in the placebo group, 14/1026 (1.4%) patients on galantamine and 3/1022 (0.3%) patients on placebo. The deaths were due to various causes.

About half of the galantamine deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death). The relevance of this finding for the treatment of patients with Alzheimer dementia is unknown. In Alzheimer dementia, placebo-controlled studies of only 6 months duration have been conducted. In these studies no increased mortality in the galantamine groups appeared.

A diagnosis of Alzheimer's dementia should be made according to current guidelines by an experienced physician. Therapy with galantamine should occur under the supervision of a physician and should only be initiated if a caregiver is available who will regularly monitor medicinal product intake by the patient.

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.

As with other cholinomimetics, galantamine should be given with caution in the following conditions:

Cardiac disorders

Because of their pharmacological action, cholinomimetics may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disturbances or in those who use medicinal products that significantly reduce heart rate concomitantly, such as digoxin and beta-blockers or for patients with an uncorrected electrolyte disturbance (e.g. hyperkalaemia, hypokalaemia).

Caution should therefore be exercised when administering galantamine to patients with cardiovascular diseases, e.g. immediate post-myocardial infarction period, new-onset atrial fibrillation, second degree heart block or greater, unstable angina pectoris or congestive heart failure, especially NYHA group III – IV.

In a pooled analysis of placebo-controlled studies in patients with Alzheimer's dementia treated with galantamine an increased incidence of certain cardiovascular adverse events were observed (see section 4.8).

Gastrointestinal disorders

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 non-steroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. The use of galantamine is not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Nervous system disorders

Although cholinomimetics are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease. In rare cases an increase in cholinergic tone may worsen Parkinsonian symptoms.

In a pooled analysis of placebo-controlled studies in patients with Alzheimer's dementia treated with galantamine cerebrovascular events were uncommonly observed (see section 4.8). This should be considered when administering galantamine to patients with cerebrovascular disease.

Respiratory, thoracic and mediastinal disorders

Cholinomimetics should be prescribed with care for patients with a history of severe asthma or obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).

Renal and urinary disorders

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

Surgical and medical procedures

Galantamine, as a cholinomimetic is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia, especially in cases of pseudocholinesterase deficiency.

Other

Prolonged Release capsules only

Galantamine prolonged-release capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Oral Tablets only

Orange yellow S aluminium lake (E110), present in the 12 mg tablet, may cause allergic reactions.

Galantamine tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Oral Solution only

Galantamine oral solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Because of its mechanism of action, galantamine should not be given concomitantly with other cholinomimetics (such as ambenonium, donepezil, neostigmine, pyridostigmine, rivastigmine or systemically administered pilocarpine). Galantamine has the potential to antagonise the effect of anticholinergic medication. Should anticholinergic medication such as atropine be abruptly stopped there is a potential risk that galantamine's effect could be exacerbated. As expected with cholinomimetics, a pharmacodynamic interaction is possible with medicinal products that significantly reduce the heart rate such as digoxin, beta-blockers, certain calcium-channel blocking agents and amiodarone. Caution should be taken with medicinal products that have potential to cause *torsades de pointes*. In such cases an ECG should be considered.

Galantamine, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia, especially in cases of pseudocholinesterase deficiency.

Pharmacokinetic interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. The possibility of clinically relevant interactions is low. However, the occurrence of significant interactions may be clinically relevant in individual cases.

Concomitant administration with food slows the absorption rate of galantamine but does not affect the extent of absorption. It is recommended that galantamine be taken with food in order to minimise cholinergic side effects.

Other medicinal products 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-treatment with ketoconazole and erythromycin (both CYP3A4 inhibitors). Therefore, during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine or fluoxetine) or CYP3A4 (e.g. ketoconazole or ritonavir) patients may experience an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the galantamine maintenance dose can be considered (see section 4.2).

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

Effect of galantamine on the metabolism of other medicinal products

Therapeutic doses of galantamine 24 mg/day had no effect on the kinetics of digoxin, although pharmacodynamic interactions may occur (see also pharmacodynamic interactions).

Therapeutic doses of galantamine 24 mg/day had no effect on the kinetics and prothrombin time of warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy

For galantamine no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

Galantamine has minor to moderate influence on the ability to drive and use machines. Symptoms include dizziness and somnolence, especially during the first weeks after initiation of treatment.

4.8 Undesirable effects

The table below reflects data obtained with galantamine in seven placebo-controlled, double-blind clinical trials (N=4457), five open-label clinical trials (N=1454), and from postmarketing spontaneous reports. The most commonly reported adverse drug reactions were nausea (25%) and vomiting (13%). They 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.

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

Frequency estimate: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); and very rare ($< 1/10,000$).

System Organ Class	Adverse Drug Reaction Frequency				
	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders			Hypersensitivity		
Metabolism and nutrition disorders		Decreased appetite; Anorexia	Dehydration		
Psychiatric disorders		Hallucination; Depression	Hallucination visual; Hallucination auditory		

System Organ Class	Adverse Drug Reaction Frequency				
	Very common	Common	Uncommon	Rare	Very rare
Nervous system disorders		Syncope; Dizziness; Tremor; Headache; Somnolence; Lethargy	Paraesthesia; Dysgeusia; Hypersomnia		
Eye disorders			Vision blurred		
Ear and labyrinth disorders			Tinnitus		
Cardiac disorders		Bradycardia	Supraventricular extrasystoles; Atrioventricular block first degree; Sinus bradycardia; Palpitations		
Vascular disorders		Hypertension	Hypotension; Flushing		
Gastrointestinal disorders	Vomiting; Nausea	Abdominal pain; Abdominal pain upper; Diarrhoea; Dyspepsia; Stomach discomfort; Abdominal discomfort	Retching		
Hepatobiliary disorders				Hepatitis	
Skin and subcutaneous tissue disorders		Hyperhidrosis			
Musculoskeletal and connective tissue disorders		Muscle spasms	Muscular weakness		
General disorders and administration site conditions		Fatigue; Asthenia; Malaise			
Investigations		Weight decreased	Hepatic enzyme increased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Class-related effects reported with acetylcholinesterase-inhibitor antidementia drugs include convulsions/seizures (see 4.4 Nervous system disorders).

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

There have been post-marketing reports of *Torsade de pointes*, QT prolongation, bradycardia ventricular tachycardia and brief loss of consciousness in association with inadvertent overdoses of galantamine. In one case where the dose was known, eight 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 i.v. is recommended, with subsequent doses based on the clinical response.

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