IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/114/003
Case No: 2025548

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Galtam 12mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **01/02/2008** until **31/01/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Galtam 12mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12 mg Galantamine (as hydrobromide).
Excipient: 148.841mg lactose monohydrate .
0.243 mg Sunset Yellow FCF Aluminium lake (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet.
Orange coloured, oval, biconvex film-coated tablets plain on both sides

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Adults/Elderly

Administration

Galantamine 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

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.

• 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.

• 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).

Children
Galantamine is not recommended for use in children.
Hepatic and renal impairment
Galantamine plasma levels may be increased in patients with moderate to severe hepatic or renal impairment. 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 b.i.d. for at least 4 weeks. In these patients, daily doses should not exceed 8 mg b.i.d.. 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 (e.g. ketoconazole) dose reductions can be considered (see section 4.5).

4.3 Contraindications

Galantamine should not be administered to patients with a known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulations. 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 warnings and precautions for use

Galantamine is indicated for a patient with mild to moderately severe dementia of 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 drug 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:

Cardiovascular conditions: 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 who use drugs that significantly reduce heart rate concomitantly, such as digoxin and betablockers 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 dementia treated with galantamine an increased incidence of certain cardiovascular adverse events were observed (see section 4.8 Undesirable effects).

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, should be monitored for symptoms. The use of galantamine is not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Neurological Conditions: cholinomimetics are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials there was no increase in incidence of convulsions with galantamine compared with placebo. 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 Undesirable effects). This should be considered when administering galantamine to patients with cerebrovascular disease.

Pulmonary Conditions: 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).
Genitourinary: the use of galantamine is not recommended in patients with urinary outflow obstruction or recovering from bladder surgery.

Anaesthesia: galantamine, as a cholinomimetic is likely to exaggerate succinylcholinetype muscle relaxation during anaesthesia.

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Galantamine antagonises the effect of anticholinergic medication. As expected with cholinomimetics, a pharmacodynamic interaction is possible with drugs that significantly reduce the heart rate (e.g. digoxin and beta blockers). Galantamine, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Pharmacokinetic interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine.

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 drugs 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, fluoxetine or fluvoxamine) or CYP3A4 (e.g. ketoconazole, ritonavir) patients may experience an increased incidence of cholinergic side effects, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the galantamine maintenance dose can be considered (see section 4.2).

Effect of galantamine on the metabolism of other drugs

Therapeutic doses of galantamine (12 mg b.i.d.) had no effect on the kinetics of digoxin and warfarin (see also pharmacodynamic interactions).

4.6 Pregnancy and lactation

Pregnancy

For galantamine no clinical data on exposed pregnancies are available. Animal studies indicate a slightly delayed development in foetuses and neonates (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation

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 may cause dizziness and somnolence, which could affect the ability to drive or use machines, especially during the first weeks after initiation of treatment.

4.8 Undesirable effects

The most common adverse events observed in clinical trials (incidence ≥5% and twice the frequency of placebo) were nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia, fatigue, dizziness, headache, somnolence and weight decrease. Nausea, vomiting and anorexia were more commonly observed in women.

Other common adverse events observed in clinical trials (incidence ≥5% and ≥placebo) were confusion, depression, fall, injury, insomnia, rhinitis and urinary tract infection.
The majority of these adverse events occurred during the titration period. Nausea and vomiting, the most frequent adverse events, lasted less than a week in most cases and the majority of patients had only one episode. Prescription of anti-emetics and ensuring adequate fluid intake may be useful in these instances.

Adverse events observed during clinical trials and post marketing experience.
Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Rhinitis Urinary tract infections			
Metabolism and nutrition disorders		Anorexia Weight decrease		Dehydration (leading to renal insufficiency and renal failure) Hypokalaemia	
Psychiatric disorders		Confusion Depression (very rarely with suicidality) Insomnia		Aggression Agitation Hallucinations	
Nervous system disorders		Dizziness Somnolence Syncope Tremor	Paraesthesia	Seizures	Worsening of Parkinsonism
Ear and labyrinth disorders			Tinnitus		
Cardiac disorders			Atrial arrhythmia Myocardial infarction Myocardial ischaemia Palpitation	Bradycardia (severe)	AV block
Vascular disorders			Cerebrovascular disease Transient ischaemic attack		Hypotension
Gastrointestinal disorders	Vomiting Nausea	Abdominal pain Diarrhoea Dyspepsia			Dysphagia Gastrointestinal bleeding
Skin and subcutaneous tissue disorders				Rash	Increased sweating
Musculoskeletal and connective tissue disorders			Leg Cramps		
General disorders and administration site conditions		Asthenia Fatigue Fever Headache Malaise			
Injury, poisoning and procedural complications		Fall Injury			

Some of these adverse events may be attributable to cholinomimetic properties of galantamine or in some cases may represent manifestations or exacerbations of the underlying disease processes common in the elderly population.

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.

In a post-marketing report, bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness were reported in association with an inadvertent ingestion of eight 4 mg tablets (32 mg total) on a single day.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidementia drugs; ATC-code: N06DA04

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

Clinical studies

The dosages of galantamine effective in placebo-controlled clinical trials with a duration of 5 to 6 months were 16, 24 and 32 mg/day. Of these doses 16 and 24 mg/day were judged to have the best benefit/risk and were retained as recommended maintenance doses. Galantamine's efficacy has been shown using outcome measures which evaluate the three major symptom complexes of the disease and a global scale: the ADAS-Cog (a performance based measure of cognition), DAD and ADCS-ADL-Inventory (measurements of basic and instrumental Activities of Daily Living), the Neuropsychiatric Inventory (a scale that measures behavioural disturbances) and the CIBIC-plus (a global assessment by an independent physician based on a clinical interview with the patient and caregiver).

Composite responder analysis based on at least 4 points improvement in ADAS-Cog/11 compared to baseline and CIBIC-plus unchanged + improved (1-4), and DAD/ADL score unchanged + improved.

	At least 4 points improvement from baseline in ADAS-Cog/11 and CIBIC-plus Unchanged+Improved							
	Change in DAD ≥0 GAL-USA-1 and GAL-INT-1 (Month 6)				Change in ADCS/ADL-Inventory ≥0 GAL-USA-10 (Month 5)			
Treatment	N	n (%) of responder	Comparison with placebo		N	n (%) of responder	Comparison with placebo	
			Diff (95%CI)	p-value†			Diff (95%CI)	p-value†
Classical ITT								
Placebo	422	21 (5.0)	-	-	273	18 (6.6)	-	-
Gal 16 mg/day	-	-	-	-	266	39 (14.7)	8.1 (3, 13)	0.003
Gal 24 mg/day	424	60 (14.2)	9.2 (5, 13)	<0.001	262	40 (15.3)	8.7 (3, 14)	0.002
Trad. LOCF *								
Placebo	412	23 (5.6)	-	-	261	17 (6.5)	-	-
Gal 16 mg/day	-	-	-	-	253	36 (14.2)	7.7 (2, 13)	0.005
Gal 24 mg/day	399	58 (14.5)	8.9 (5, 13)	<0.001	253	40 (15.8)	9.3 (4, 15)	0.001

† CMH test of difference from placebo.
* LOCF: Last Observation Carried Forward.

5.2 Pharmacokinetic properties

Galantamine is an alkalinic compound with one ionisation constant (pKa 8.2). It is slightly lipophilic and has a partition coefficient (Log P) between n-octanol/buffer solution (pH 12) of 1.09. The solubility in water (pH 6) is 31 mg/ml. Galantamine has three chiral centres, the S, R, S-form is the naturally occurring form. Galantamine is partially metabolised by various cytochromes, mainly CYP2D6 and CYP3A4. Some of the metabolites formed during the degradation of galantamine have been shown to be active in vitro but are of no importance *in vivo.*

GENERAL characteristics of galantamine

Absorption
The absorption is rapid, with a tmax of about 1 hour after both tablets and oral solution. The absolute bioavailability of galantamine is high, 88.5 ± 5.4%. The presence of food delays the rate of absorption and reduces Cmax by about 25%, without affecting the extent of absorption (AUC).

Distribution
The mean volume of distribution is 175 L. Plasma protein binding is low, 18%.

Metabolism
Up to 75% of galantamine dosed is eliminated via metabolism. In vitro studies indicate that CYP2D6 is involved in the formation of O-desmethylgalantamine and CYP3A4 is involved in the formation of N-oxide-galantamine. The levels of excretion of total radioactivity in urine and faeces were not different between poor and extensive CYP2D6 metabolisers. In plasma from poor and extensive metabolisers, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. 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 and 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. In vitro studies indicated that the inhibition potential of galantamine with respect to the major forms of human cytochrome P450 is very low.

Elimination
Galantamine plasma concentration declines bi-exponentially, with a terminal half-life in the order of 7-8 h in healthy subjects. Typical oral clearance in the target population is about 200 mL/min with intersubject variability of 30% as derived from the population analysis. Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 90-97% of the radioactivity is recovered in urine and 2.2 – 6.3% in faeces.

After i.v. infusion and oral administration, 18-22% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of 68.4 ± 22.0 ml/min, which represents 20-25% of the total plasma clearance.

Dose-linearity
After repeated oral dosing of 12 and 16 mg galantamine b.i.d., mean trough and peak plasma concentrations fluctuated between 29 – 97 ng/ml and 42 – 137 ng/ml. The pharmacokinetics of galantamine are linear in the dose range of 4 - 16 mg b.i.d. In patients taking 12 or 16 mg b.i.d., no accumulation of galantamine was observed between months 2 and 6.

Characteristics in patients
Data from clinical trials in patients indicate that the plasma concentrations of galantamine in patients with Alzheimer's disease are 30-40% higher than in healthy young subjects. Based upon the population pharmacokinetic analysis, clearance in female subjects is 20% lower as compared to males. No major effects of age per se or race are found on the galantamine clearance. The galantamine clearance in poor metabolisers of CYP2D6 is about 25% lower than in extensive metabolisers, but no bimodality in the population is observed. Therefore, the metabolic status of the patient is not considered to be of clinical relevance in the overall population.

The pharmacokinetics of galantamine in subjects with mild hepatic impairment (Child-Pugh score of 5-6) were comparable to those in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% (see section 4.2).

Elimination of galantamine decreases with decreasing creatinine clearance as observed in a study with renally impaired subjects. Compared to Alzheimer patients, peak and trough plasma concentrations are not increased in patients with a creatinine clearance of ≥9 ml/min. Therefore, no increase in adverse events is expected and no dosage adjustments are needed (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship
No apparent correlation between average plasma concentrations and efficacy parameters (i.e. Change in ADAS-Cog11 and CIBIC-plus at Month 6) were observed in the large Phase III trials with a dose-regimen of 12 and 16 mg b.i.d. These results indicate that maximal effects may be obtained at the studied doses.
Plasma concentrations in patients experiencing syncope were within the same range as in the other patients at the same dose.
The occurrence of nausea is shown to correlate with higher peak plasma concentrations (see section 4.5).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans other than those expected from the pharmacodynamic effect of galantamine. This assumption is based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Reproduction toxicity studies showed a slight delay in development in rats and rabbits, at doses, which are below the threshold of toxicity in the pregnant females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose Monohydrate
Citric acid Monohydrate
Talc
Magnesium stearate
Silica, Colloidal Anhydrous
Sodium Starch Glycolate

Film-coating:
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Macrogol
Triacetin

Iron Oxide Red (E172)
Sunset Yellow FCF Aluminium lake (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

1 year

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Alu/Alu blister: 56, 168 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co.Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/114/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st February 2008

10 DATE OF REVISION OF THE TEXT