Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

REMINYL 4 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 mg tablet contains 4 mg galantamine (as hydrobromide).

Excipients with known effect:

Lactose monohydrate 38.59 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

4 mg tablet: Off-white, circular, biconvex tablets with the inscription “JANSSEN” on one side and “G4” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology

Adults/Elderly

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 4 weeks.

Maintenance dose

The tolerance and dosing of galantamine should be reassessed on a regular basis, preferably within 3 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.

Treatment withdrawal

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

Renal impairment

Galantamine plasma concentrations may be increased in patients with moderate to severe renal impairment (see section 5.2)

For patients with a creatinine clearance ≥9 ml/min, no dosage adjustment is required.

The use of galantamine is contraindicated in patients with creatinine clearance less than 9 ml/min(see section 4.3).

Hepatic impairment

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment (see section 5.2).

In patients with moderately impaired hepatic function (Child-Pugh score 7-9), based on pharmacokinetic modelling, it is recommended that dosing should begin with 4 mg once daily, preferably taken in the morning, for at least 1 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 renal impairment (creatinine clearance less than 9 ml/min), the use of galantamine is contraindicated (see section 4.3).

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

Concomitant treatment

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

Paediatric population

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

Method of administration

Reminyl tablets should be administered orally, twice a day, preferably with morning and evening meals. Ensure adequate fluid intake during treatment (see section 4.8)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

Types of dementia

Reminyl 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 2 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's dementia is unknown.

No increased mortality in the galantamine group was observed in a long−term, randomized, placebo−controlled study in 2045 patients with mild to moderate Alzheimer´s disease. The mortality rate in the placebo group was significantly higher than in the galantamine group. There were 56/1021 (5.5%) deaths in patients on placebo and 33/1024 (3.2%) deaths in patients on galantamine (hazard ratio and 95% confidence intervals of 0.58 [0.37 – 0.89]; p=0.011).

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.

Serious skin reactions

Serious skin reactions (Stevens−Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in patients receiving Reminyl (see section 4.8). It is recommended that patients be informed about the signs of serious skin reactions, and that use of Reminyl be discontinued at the first appearance of skin rash.

Weight monitoring

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

Conditions requiring caution

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 , including bradycardia and all types of atrioventricular node block (see section 4.8). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or 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
Seizures have been reported with galantamine (see section 4.8). . 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.

Excipients of Reminyl film- coated tablets

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

Reminyl 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.

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 effects 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 Reminyl 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 Reminyl XL 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.

Breast- feeding

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.

Fertility

The effect of galantamine on human fertility has not been evaluated

4.7 Effects on ability to drive and use machines

Galantamine has a 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 Reminyl in eight placebo-controlled, double-blind clinical trials (N=6,502), five open-label clinical trials (N=1,454), and from postmarketing spontaneous reports. The most commonly reported adverse reactions were nausea (21%) and vomiting (11%). 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.

Frequency estimate: 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); and very rare (<1/10,000).

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

Nervous system disorders		Syncope; Dizziness; Tremor; Headache; Somnolence; Lethargy	Paraesthesia; Dysgeusia; Hypersomnia Seizures*	
Eye disorders			Vision blurred	
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders		Bradycardia	Supraventricular extrasystoles; Atrioventricular block first degree; Sinus bradycardia; Palpitations	Atrioventricular block complete
Vascular disorders		Hypertension	Hypotension; Flushing	
Gastrointestinal disorders	Vomiting; Nausea	Abdominal pain; Abdominal pain upper; Diarrhoea; Dyspepsia; Abdominal discomfort	Retching	
Hepatobiliary disorders				Hepatitis
Skin and subcutaneous tissue disorders			Hyperhidrosis	Stevens−Johnson Syndrome; Acute generalized exanthematous pustulosis; Erythema multiforme
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; Laceration		

* Class-related effects reported with acetylcholinesterase-inhibitor antidementia drugs include convulsions/seizures (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.hpra.ie/
E-mail: medsafety@hpra.ie

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 intravenously is recommended, with subsequent doses based on the clinical response.

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

Mechanism of action

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

Clinical studies

The dosages of 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 determined to have the best benefit/risk relationship and are the recommended maintenance doses. The efficacy of galantamine 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. See table below.

	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/ADLInventory ≥ 0 GAL-USA-10 (Month 5)			
			Comparison with placebo				Comparison with placebo	
Treatment	N	n (%) of responder	Diff (95% CI)	p-value†	N	n (%) of responder	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
Traditional. 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

ITT: Intent To Treat

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

Vascular dementia or Alzheimer's disease with cerebrovascular disease

The results of a 26-week double-blind placebo-controlled trial, in which patients with vascular dementia and patients with Alzheimer's disease and concomitant cerebrovascular disease ("mixed dementia") were included, indicate that the symptomatic effect of galantamine is maintained in patients with Alzheimer's disease and concomitant cerebrovascular disease (see section 4.4,). In a post-hoc subgroup analysis, no statistically significant effect was observed in the subgroup of patients with vascular dementia alone.

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

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*.

Absorption
The absorption is rapid, with a t_{max} 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%.

Biotransformation
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 intravenous 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 twice-daily as tablets, 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 twice-daily. In patients taking 12 or 16 mg twice-daily, no accumulation of galantamine was observed between months 2 and 6.

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

Special populations
Renal impairment
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).

Hepatic impairment
The pharmacokinetics of galantamine in subjects with mild hepatic impairment (Child-Pugh score of 5-6) were comparable to those in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh score of 7-9), AUC

and half-life of galantamine were increased by about 30% (see 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 twice daily.
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

Non-clinical data suggest no special hazard for humans 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 that are below the threshold of toxicity in the pregnant females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Colloidal anhydrous silica
Crospovidone
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

Film-coating:
Hypromellose
Propylene glycol
Talc
Titanium dioxide (E171)
Yellow ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

4 mg tablets: 14 or 56 film-coated tablets (PVC-PE-PVDC/Aluminium blister).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Limited
1 Kingdom Street
London, W2 6BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0535/006/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2000

Date of last renewal: 01 March 2010

10 DATE OF REVISION OF THE TEXT

November 2017