

**IRISH MEDICINES BOARD ACT 1995, as amended**

**Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended**

**PA0749/022/003**

Case No: 2082897

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

**Teva Pharma B.V.**

**Computerweg 10, 3542 DR Utrecht, Netherlands**

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

**Galantamine Teva 12mg Film-coated Tablets**

the particulars of which are set out in 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 **01/09/2010** until **18/12/2012**.

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

Galantamine Teva 12mg Film-coated Tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12 mg galantamine (as hydrobromide)

##### Excipients:

Each film-coated tablet contains 77.621 mg lactose monohydrate and 0.194 mg sunset yellow FCF (E110).

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Film-coated tablets.

Orange, film coated capsule shaped tablet, debossed "7417" on one side and "93" on the other side.

#### 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

Oral use.

##### Adults/Elderly

##### Administration

Galantamine should be administered twice a day, preferably with morning and evening meals. The tablets should be swallowed whole with water and must not be broken, crushed or chewed. 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 due to a lack of data on safety and efficacy.

### 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**

- Hypersensitivity to galantamine hydrobromide 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 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 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 who use medicinal products 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).

#### *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 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). 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 succinylcholinetype muscle relaxation during anaesthesia, especially in cases of pseudocholinesterase deficiency.

#### *Other*

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

Sunset yellow FCF (E110) may cause allergic reactions.

## **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 treatment 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 and 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 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 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 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 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.

#### 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 has minor or 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 most commonly reported adverse reactions were nausea and vomiting.

They occurred mainly during the titration period, 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.

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

Adverse events observed during clinical trials and post marketing experience.

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Rhinitis Urinary tract infections			
Metabolism and nutrition disorders		Decreased appetite Anorexia	Dehydration	Hypokalaemia	
Psychiatric disorders		Hallucination Confusion Depression (very rarely with suicidality) Insomnia	Hallucination visual Hallucination auditory	Aggression Agitation	
Nervous system disorders		Syncope Dizziness Tremor Headache Somnolence Lethargy	Paraesthesia Dysgeusia Hypersomnia		Worsening of Parkinsonism Seizures
Eye disorders			Vision blurred		
Ear and labyrinth disorders			Tinnitus		
Cardiac disorders		Bradycardia	Supraventricular extrasystoles Atrioventricular block first degree Sinus bradycardia Myocardial infarction Myocardial ischaemia Palpitation		
Vascular disorders		Hypertension	Hypotension Flushing Cerebrovascular disease Transient ischaemic attack		
Gastrointestinal	Vomiting	Abdominal	Retching		Dysphagia

disorders	Nausea	pain Abdominal pain upper Diarrhoea Dyspepsia Stomach discomfort Abdominal discomfort			Gastrointestinal bleeding
Hepatobiliary disorders				Hepatitis	
Skin and subcutaneous tissue disorders		Hyperhidrosis		Rash	
Musculoskeletal and connective tissue disorders		Muscle spasms	Muscular weakness Leg Cramps		
General disorders and administration site conditions		Fatigue Asthenia Fever Malaise			
Investigations		Weight decreased	Hepatic enzyme increased		
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.

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 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: Anticholinesterases.

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 are the 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/11 (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.

Treatment	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)			
	n	n (%) of responder	Comparison with placebo		n	n (%) of responder	Comparison with placebo	
Diff (95% CI)			p-value <sup>†</sup>	Diff (95% CI)			p-value <sup>†</sup>	
<b>Classical ITT<sup>#</sup></b>								
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
<b>Traditional LOCF *</b>								
Placebo	412	23 (5.6)	-	-	261	17 (6.5)	-	-

Gal mg/day	16	-	-	-	-	253	36 (14.2)	7.7 (2, 13)	0.005
Gal mg/day	24	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									

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, Nervous system disorders). 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 alkaline 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  $t_{max}$  of about 1 hour after both tablets and oral solution. The absolute bioavailability of galantamine is high,  $88.5 \pm 5.4\%$ . The presence of food delays the rate of absorption and reduces  $C_{max}$  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  $^3\text{H}$ -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  $68.4 \pm 22.0$  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, primarily due to the advanced age and reduced kidney function. 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  $\geq 9$  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  
Microcrystalline cellulose  
Crospovidone  
Colloidal anhydrous silica  
Magnesium stearate

#### *Coating:*

Polyvinyl alcohol

Titanium Dioxide (E171)  
Macrogol 4000  
Talc  
Iron oxide yellow (E172)  
Iron oxide red (E172)  
Sunset yellow FCF aluminium lake (E110)  
Allura red AC aluminium lake (E129)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf Life**

30 months.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

PVC/PE/PVdC -Aluminium blisters.

B blister packs of 1, 14, 30, 56, 60, 100, 112 & 168 film-coated tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

No special requirements

## **7 MARKETING AUTHORISATION HOLDER**

Teva Pharma BV  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

## **8 MARKETING AUTHORISATION NUMBER**

PA 749/22/3

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19<sup>th</sup> December 2007

## **10 DATE OF REVISION OF THE TEXT**

September 2010