1. NAME OF THE MEDICINAL PRODUCT

AZILECT 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg rasagiline (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, flat, bevelled tablets, debossed with “GIL” and “1” underneath on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZILECT is indicated in adults for the treatment of idiopathic Parkinson’s disease as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

4.2 Posology and method of administration

Posology

The recommended dose of rasagiline is 1 mg (one tablet of AZILECT) once daily, to be taken with or without levodopa.

Elderly
No change in dose is required for elderly patients (see section 5.2).

Hepatic impairment
Rasagiline is contraindicated in patients with severe hepatic impairment (see section 4.3). Rasagiline use in patients with moderate hepatic impairment should be avoided. Caution should be used when initiating treatment with rasagiline in patients with mild hepatic impairment. In case patients progress from mild to moderate hepatic impairment rasagiline should be stopped (see section 4.4 and 5.2).

Renal impairment
No special precautions are required in patients with renal impairment.

Paediatric population
The safety and efficacy of AZILECT in children and adolescents have not been established. There is no relevant use of AZILECT in the paediatric population in the indication Parkinson’s disease.

Method of administration

For oral use.
AZILECT may be taken with or without food.

4.3 Contraindications

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

Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) or pethidine (see section 4.5). At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine.

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Concomitant use of rasagiline with other medicinal products

The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided (see section 4.5). At least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with rasagiline. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine.

The concomitant use of rasagiline and dextromethorphan or sympathomimetics such as those present in nasal and oral decongestants or cold medicinal product containing ephedrine or pseudoephedrine is not recommended (see section 4.5).

Concomitant use of rasagiline and levodopa
Since rasagiline potentiates the effects of levodopa, the adverse reactions of levodopa may be increased and pre-existing dyskinesia exacerbated. Decreasing the dose of levodopa may ameliorate this adverse reaction.

There have been reports of hypotensive effects when rasagiline is taken concomitantly with levodopa. Patients with Parkinson's disease are particularly vulnerable to the adverse reactions of hypotension due to existing gait issues.

Dopaminergic effects

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes
Rasagiline may cause daytime drowsiness, somnolence, and, occasionally, especially if used with other dopaminergic medicinal products - falling asleep during activities of daily living. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with rasagiline. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section 4.7).

Impulse control disorders (ICDs)
ICDs can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Similar reports of ICDs have also been received post-marketing with rasagiline. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware of the behavioural symptoms of impulse control disorders that were observed in patients treated with rasagiline, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

Melanoma

A retrospective cohort study suggested a possibly increased risk of melanoma with the use of rasagiline, especially in patients with longer duration of rasagiline exposure and/or with the higher cumulative dose of rasagiline. Any suspicious skin lesion should be evaluated by a specialist. Patients should therefore be advised to seek medical review if a new or changing skin lesion is identified.

Hepatic impairment

Caution should be used when initiating treatment with rasagiline in patients with mild hepatic impairment. Rasagiline use in patients with moderate hepatic impairment should be avoided. In case patients progress from mild to moderate hepatic impairment, rasagiline should be stopped (see section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

MAO Inhibitors

Rasagiline is contraindicated along with other MAO inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crises (see section 4.3).

Pethidine

Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors including another selective MAO-B inhibitor. The concomitant administration of rasagiline and pethidine is contraindicated (see section 4.3).

Sympathomimetics

With MAO inhibitors there have been reports of medicinal product interactions with the concomitant use of sympathomimetic medicinal products. Therefore, in view of the MAO inhibitory activity of rasagiline, concomitant administration of rasagiline and sympathomimetics such as those present in nasal and oral decongestants or cold medicinal products, containing ephedrine or pseudoephedrine, is not recommended (see section 4.4).

Dextromethorphan

There have been reports of medicinal product interactions with the concomitant use of dextromethorphan and non-selective MAO inhibitors. Therefore, in view of the MAO inhibitory activity of rasagiline, the concomitant administration of rasagiline and dextromethorphan is not recommended (see section 4.4).

SNRI/SSRI/tri- and tetracyclic antidepressants

The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided (see section 4.4).

For concomitant use of rasagiline with selective serotonin reuptake inhibitors (SSRIs)/selective serotonin-norepinephrine reuptake inhibitors (SNRIs) in clinical trials, see section 4.8.

Serious adverse reactions have been reported with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors. Therefore, in view of the MAO inhibitory activity of rasagiline, antidepressants should be administered with caution.

Agents that affect CYP1A2 activity

In vitro metabolism studies have indicated that cytochrome P450 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of rasagiline.

CYP1A2 inhibitors
Co-administration of rasagiline and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC of rasagiline by 83%. Co-administration of rasagiline and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either product. Thus, potent CYP1A2 inhibitors may alter rasagiline plasma levels and should be administered with caution.

CYP1A2 inducers
There is a risk that the plasma levels of rasagiline in smoking patients could be decreased, due to induction of the metabolising enzyme CYP1A2.

Other cytochrome P450 isoenzymes

In vitro studies showed that rasagiline at a concentration of 1 μg/ml (equivalent to a level that is 160 times the average C_{max} ~ 5.9-8.5 ng/ml in Parkinson's disease patients after 1 mg rasagiline multiple dosing), did not inhibit cytochrome P450 isoenzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes (see section 5.3).

Levodopa and other Parkinson's disease medicinal products

In Parkinson's disease patients receiving rasagiline as adjunct therapy to chronic levodopa treatment, there was no clinically significant effect of levodopa treatment on rasagiline clearance.

Concomitant administration of rasagiline and entacapone increased rasagiline oral clearance by 28%.

Tyramine/rasagiline interaction

Results of five tyramine challenge studies (in volunteers and Parkinson's disease patients), together with results of home monitoring of blood pressure after meals (of 464 patients treated with 0.5 or 1 mg/day of rasagiline or placebo as adjunct therapy to levodopa for six months without tyramine restrictions), and the fact that there were no reports of tyramine/rasagiline interaction in clinical studies conducted without tyramine restriction, indicate that rasagiline can be used safely without dietary tyramine restrictions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of rasagiline in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of rasagiline during pregnancy.

Breast-feeding

Non-clinical data indicate that rasagiline inhibits prolactin secretion and thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk. Caution should be exercised when rasagiline is administered to a breast-feeding mother.

Fertility

No human data on the effect of rasagiline on fertility are available. Non-clinical data indicate that rasagiline has no effect on fertility.

4.7 Effects on ability to drive and use machines

In patients experiencing somnolence/sudden sleep episodes, rasagiline may have major influence on the ability to drive and use machines.
Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that rasagiline does not affect them adversely.

Patients being treated with rasagiline and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until they have gained sufficient experience with rasagiline and other dopaminergic medications to gauge whether or not it affects their mental and/or motor performance adversely.

If increased somnolence or new episodes of falling asleep during activities of daily living (e.g. watching television, passenger in a car, etc.) are experienced at any time during treatment, the patients should not drive or participate in potentially dangerous activities.
Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of rasagiline.

Patients should be cautioned about possible additive effects of sedating medicinal products, alcohol, or other central nervous system depressants (e.g. benzodiazepines, antipsychotics, antidepressants) in combination with rasagiline, or when taking concomitant medications that increase plasma levels of rasagiline (e.g. ciprofloxacin) (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In clinical studies in Parkinson's disease patients the most commonly reported adverse reactions were: headache, depression, vertigo, and flu (influenza and rhinitis) in monotherapy; dyskinesia, orthostatic hypotension, fall, abdominal pain, nausea and vomiting, and dry mouth in adjunct to levodopa therapy; musculoskeletal pain, as back and neck pain, and arthralgia in both regimens. These adverse reactions were not associated with an elevated rate of drug discontinuation.

Tabulated list of adverse reactions

Adverse reactions are listed below in Tables 1 and 2 by system organ class and frequency using the following conventions: 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).

Monotherapy
The tabulated list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies, in patients receiving 1 mg/day rasagiline.

System Organ Class	Very common	Common	Uncommon	Not known
Infections and infestations		Influenza		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Skin carcinoma		
Blood and lymphatic system disorders		Leucopenia		
Immune system disorders		Allergy		
Metabolism and nutrition disorders			Decreased appetite	

System Organ Class	Very common	Common	Uncommon	Not known
Psychiatric disorders		Depression, Hallucinations*		Impulse control disorders*
Nervous system disorders	Headache		Cerebrovascular accident	Serotonin syndrome*, Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes*
Eye disorders		Conjunctivitis		
Ear and labyrinth disorders		Vertigo		
Cardiac disorders		Angina pectoris	Myocardial infarction	
Vascular disorders				Hypertension*
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal disorders		Flatulence		
Skin and subcutaneous tissue disorders		Dermatitis	Vesiculobullous rash	
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Neck pain, Arthritis		
Renal and urinary disorders		Urinary urgency		
General disorders and administration site conditions		Fever, Malaise		
*See section description of selected adverse reactions				

Adjunct Therapy
The tabulated list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies in patients receiving 1 mg/day rasagiline.

System Organ Class	Very common	Common	Uncommon	Not known
Neoplasms benign, malignant and unspecified			Skin melanoma*	
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders		Hallucinations*, Abnormal dreams	Confusion	Impulse control disorders*
Nervous system	Dyskinesia	Dystonia,	Cerebrovascular	Serotonin

System Organ Class	Very common	Common	Uncommon	Not known
disorders		Carpal tunnel syndrome, Balance disorder	accident	syndrome*, Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes*
Cardiac disorders			Angina pectoris	
Vascular disorders		Orthostatic hypotension*		Hypertension*
Gastrointestinal disorders		Abdominal pain, Constipation, Nausea and vomiting, Dry mouth		
Skin and subcutaneous tissue disorders		Rash		
Musculoskeletal and connective tissue disorders*		Arthralgia, Neck pain		
Investigations		Decreased weight		
Injury, poisoning and procedural complications		Fall		
*See section description of selected adverse reactions				

Description of selected adverse reactions

Orthostatic hypotension
In blinded placebo-controlled studies, severe orthostatic hypotension was reported in one subject (0.3%) in the rasagiline arm (adjunct studies), none in the placebo arm. Clinical trial data further suggest that orthostatic hypotension occurs most frequently in the first two months of rasagiline treatment and tends to decrease over time.

Hypertension
Rasagiline selectively inhibits MAO-B and is not associated with increased tyramine sensitivity at the indicated dose (1 mg/day). In blinded placebo-controlled studies (monotherapy and adjunct) severe hypertension was not reported in any subjects in the rasagiline arm. In the post-marketing period, cases of elevated blood pressure, including rare serious cases of hypertensive crisis associated with ingestion of unknown amounts of tyramine-rich foods, have been reported in patients taking rasagiline. In post-marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking rasagiline.

Impulse control disorders
One case of hypersexuality was reported in monotherapy placebo-controlled study. The following were reported during post-marketing exposure with unknown frequency: compulsions, compulsive shopping, dermatillomania, dopamine dysregulation syndrome, impulse-control disorder, impulsive behaviour, kleptomania, theft, obsessive thoughts, obsessive-compulsive disorder, stereotypy, gambling, pathological gambling, libido increased, hypersexuality, psychosexual disorder, sexually inappropriate behaviour. Half of the reported ICD cases were assessed as serious. Only single cases of reported cases had not recovered at the time they were reported.

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes
Excessive daily sleepiness (hypersomnia, lethargy, sedation, sleep attacks, somnolence, sudden onset of sleep) can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of excessive daily sleepiness has been reported post-marketing with rasagiline. Cases of patients, treated with rasagiline and other dopaminergic medicinal products, falling asleep while engaged in activities of daily living have been reported. Although many of these patients reported somnolence while on rasagiline with other dopaminergic medicinal products, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported more than 1-year after initiation of treatment.

Hallucinations
Parkinson's disease is associated with symptoms of hallucinations and confusion. In post-marketing experience, these symptoms have also been observed in Parkinson's disease patients treated with rasagiline.

Serotonin syndrome
Rasagiline clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with rasagiline, but the following antidepressants and doses were allowed in the rasagiline trials: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily, and paroxetine ≤ 30 mg/daily (see section 4.5).

In the post-marketing period, cases of potentially life-threating serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus have been reported by patients treated with antidepressants, meperidine, tramadol, methadone, or propoxyphene concomitantly with rasagiline.

Malignant melanoma
Incidence of skin melanoma in placebo-controlled clinical studies was 2/380 (0.5%) in rasagiline 1 mg as adjacent to levodopa therapy group vs. 1/388 (0.3%) incidence in placebo group. Additional cases of malignant melanoma were reported during post-marketing period. These cases were considered serious in all reports.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms reported following overdose of rasagiline in doses ranging from 3 mg to 100 mg included hypomania, hypertensive crisis and serotonin syndrome.

Overdose can be associated with significant inhibition of both MAO-A and MAO-B. In a single-dose study healthy volunteers received 20 mg/day and in a ten-day study healthy volunteers received 10 mg/day. Adverse reactions were mild or moderate and not related to rasagiline treatment. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of rasagiline, there were reports of cardiovascular adverse reactions (including hypertension and postural hypotension) which resolved following treatment discontinuation. These symptoms may resemble those observed with non-selective MAO inhibitors.

Management

There is no specific antidote. In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson-Drugs, monoamine oxidase -B inhibitors, ATC code: N04BD02

Mechanism of action

Rasagiline was shown to be a potent, irreversible MAO-B selective inhibitor, which may cause an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

1-Aminoindan is an active major metabolite and it is not a MAO-B inhibitor.

Clinical efficacy and safety

The efficacy of rasagiline was established in three studies: as monotherapy treatment in study I and as adjunct therapy to levodopa in the studies II and III.

Monotherapy
In study I, 404 patients were randomly assigned to receive placebo (138 patients), rasagiline 1 mg/day (134 patients) or rasagiline 2 mg/day (132 patients) and were treated for 26 weeks, there was no active comparator.
In this study, the primary measure of efficacy was the change from baseline in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS, parts I-III). The difference between the mean change from baseline to week 26/termination (LOCF, Last Observation Carried Forward) was statistically significant (UPDRS, parts I-III: for rasagiline 1 mg compared to placebo -4.2, 95% CI [-5.7, -2.7]; $p<0.0001$; for rasagiline 2 mg compared to placebo -3.6, 95% CI [-5.0, -2.1]; $p<0.0001$, UPDRS Motor, part II: for rasagiline 1 mg compared to placebo -2.7, 95% CI [-3.87, -1.55], $p<0.0001$; for rasagiline 2 mg compared to placebo -1.68, 95% CI [-2.85, -0.51], $p=0.0050$). The effect was evident, although its magnitude was modest in this patient population with mild disease. There was a significant and beneficial effect in quality of life (as assessed by PD-QUALIF scale).

Adjunct therapy
In study II, patients were randomly assigned to receive placebo (229 patients), or rasagiline 1 mg/day (231 patients) or the catechol-O–methyl transferase (COMT) inhibitor, entacapone, 200 mg taken along with scheduled doses of levodopa (LD)/decarboxylase inhibitor (227 patients), and were treated for 18 weeks. In study III, patients were randomly assigned to receive placebo (159 patients), rasagiline 0.5 mg/day (164 patients), or rasagiline 1 mg/day (149 patients), and were treated for 26 weeks.
In both studies, the primary measure of efficacy was the change from baseline to treatment period in the mean number of hours that were spent in the "OFF" state during the day (determined from "24-hour" home diaries completed for 3 days prior to each of the assessment visits).

In study II, the mean difference in the number of hours spent in the "OFF" state compared to placebo was -0.78h, 95% CI [-1.18, -0.39], $p=0.0001$. The mean total daily decrease in the OFF time was similar in the entacapone group (-0.80h, 95% CI [-1.20, -0.41], $p<0.0001$) to that observed in the rasagiline 1 mg group. In study III, the mean difference compared to placebo was -0.94h, 95% CI [-1.36, -0.51], $p<0.0001$. There was also a statistically significant improvement over placebo with the rasagiline 0.5 mg group, yet the magnitude of improvement was lower. The robustness of the results

for the primary efficacy endpoint, was confirmed in a battery of additional statistical models and was demonstrated in three cohorts (ITT, per protocol and completers).
The secondary measures of efficacy included global assessments of improvement by the examiner, Activities of Daily Living (ADL) subscale scores when OFF and UPDRS motor while ON. Rasagiline produced statistically significant benefit compared to placebo.

5.2 Pharmacokinetic properties

Absorption

Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%.
Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the medicinal product is taken with a high fat meal. Because AUC is not substantially affected, rasagiline can be administered with or without food.

Distribution

The mean volume of distribution following a single intravenous dose of rasagiline is 243 l. Plasma protein binding following a single oral dose of ^{14}C-labelled rasagiline is approximately 60 to 70%.

Biotransformation

Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield: 1-aminoindan, 3-hydroxy-N-propargyl-1 aminoindan and 3-hydroxy-1-aminoindan. *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on cytochrome P450 system, with CYP1A2 being the major iso-enzyme involved in rasagiline metabolism. Conjugation of rasagiline and its metabolites was also found to be a major elimination pathway to yield glucuronides. *Ex vivo* and *in vitro* experiments demonstrate that rasagiline is neither inhibitor nor inducer of major CYP450 enzymes (see section 4.5).

Elimination

After oral administration of ^{14}C-labelled rasagiline, elimination occurred primarily via urine (62.6%) and secondarily via faeces (21.8%), with a total recovery of 84.4% of the dose over a period of 38 days. Less than 1% of rasagiline is excreted as unchanged product in urine.

Linearity/non-linearity

Rasagiline pharmacokinetics is linear with dose over the range of 0.5-2 mg in Parkinson's disease patients. Its terminal half-life is 0.6-2 hours.

Hepatic impairment

In subjects with mild hepatic impairment, AUC and C_{max} were increased by 80% and 38%, respectively. In subjects with moderate hepatic impairment, AUC and C_{max} were increased by 568% and 83%, respectively (see section 4.4).

Renal impairment

Rasagiline's pharmacokinetics characteristics in subjects with mild (CLcr 50-80 ml/min) and moderate (CLcr 30-49 ml/min) renal impairment were similar to healthy subjects.

Elderly

Age has little influence on rasagiline pharmacokinetics in the elderly (> 65 years) (see section 4.2)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on the standard studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, reproduction and development.

Rasagiline did not present genotoxic potential *in vivo* and in several *in vitro* systems using bacteria or hepatocytes. In the presence of metabolite activation rasagiline induced an increase of chromosomal aberrations at concentrations with excessive cytotoxicity which are unattainable at the clinical conditions of use.

Rasagiline was not carcinogenic in rats at systemic exposure, 84 – 339 times the expected plasma exposures in humans at 1 mg/day. In mice, increased incidences of combined bronchiolar/alveolar adenoma and/or carcinoma were observed at systemic exposures, 144 – 213 times the expected plasma exposure in humans at 1 mg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize starch
Pregelatinised maize starch
Colloidal anhydrous silica
Stearic acid
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years
Bottles: 3 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Blisters

Aluminium/aluminium blister packs of 7, 10, 28, 30, 100 or 112 tablets.
Aluminium/aluminium perforated unit dose blister packs of 10 x 1, 30 x 1 and 100 x 1 tablets.

Bottles

White, high-density polyethylene bottle with or without a child-resistant cap containing 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/304/001-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2005
Date of latest renewal: 21 September 2009

10. DATE OF REVISION OF THE TEXT

03/09/2020

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu