PH-120-01-1-13407 TE

PHYSICIAN'S INFORMATION LEAFLET

Rasagiline mesilate

Azilect® 1 mg tablet

1. NAME OF THE MEDICINAL PRODUCT
AZILECT® 1 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1 mg Rasagiline (as mesilate)

3. PHARMACEUTICAL FORM
White to off-white, round, flat, beveled 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 for the treatment of Parkinson's disease

4.2 Posology and method of administration
Rasagiline is administered orally, at a dose of 1 mg once daily with or without levodopa. It may be taken with or without food.

Elderly: No change in dose is required for elderly patients.

Pediatric population: Rasagiline is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Patients with hepatic impairment: Rasagiline use in patients with severe hepatic impairment is contraindicated. 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.

Patient with renal impairment: No change in dose is required for renal impairment.

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

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

Rasagiline is contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and precautions for use
The concomitant use of Rasagiline and fluoxetine or fluvoxamine should be avoided. 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.

Impulse control disorders (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.

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.

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.

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.

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes

Rasagiline may cause daytime drowsiness, somnolence, and occasionally, especially if used with other dopaminergic medications - 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 "Effects on ability to drive and use machines").

4.5 Interaction with other medicinal products and other forms of interaction
There are a number of known interactions between non selective MAO inhibitors and other medicinal products.

Rasagiline must not be administered 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.

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.

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.

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.

The concomitant use of Rasagiline and fluoxetine or fluvoxamine should be avoided.

For concomitant use of Rasagiline with selective serotonin reuptake inhibitors (SSRIs/selective serotonin-norepinephrine reuptake inhibitors (SNRIs) in clinical trials.

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

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

In vitro, metabolism studies have indicated that cytochrome P450 1 A2 (CYP1 A2) is the major enzyme responsible for the metabolism of Rasagiline. Co-administration of Rasagiline and ciprofloxacin (an inhibitor of CYP1 A2) 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 CYP1 A2 inhibitors may alter Rasagiline plasma levels and should be administered with caution.

There is a risk that the plasma levels of Rasagiline in smoking patients could be decreased, due to induction of the metabolizing enzyme CYP1 A2.

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 therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

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

Tyramine/ Rasagiline interaction: Results of five tyramine challenge studies (in volunteers and PD 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/ Azilect® (Rasagiline mesilate) 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
For Rasagiline no clinical data on exposed pregnancies is available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post natal development. Caution should be exercised when prescribing to pregnant women.

Experimental data indicated 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.

4.7 Effects on ability to drive and use machines
Rasagiline may affect the ability to drive and use machines.

Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonable 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 medications, 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 "Special warnings and precautions for use").

4.8 Undesirable effects
In the Rasagiline clinical program overall, 1,361 patients were treated with Rasagiline for 3,076.4 patient years. In the double blind placebo controlled studies, 529 patients were treated with Rasagiline 1 mg/day for 212 patient years and 539 patients received placebo for 213 patient years.

Monotherapy
The list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies, in patients receiving 1 mg/day Rasagiline (rasagiline group n=149, placebo group n=151).

Adverse reactions with at least 2% difference over placebo are marked in *italics*. In parentheses is the adverse reaction incidence (% of patients) in Rasagiline) vs. placebo, respectively.

Adverse reactions are ranked under headings of frequency using the following conventions: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000).

Infections and infestations
Common: *influenza (4.7% vs. 0.7%)*
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: skin carcinoma (1.3% vs. 0.7%)
Blood and lymphatic system disorders
Common: leucopenia (1.3% vs. 0%)
Immune system disorders
Common: allergy (1.3% vs. 0.7%)
Metabolism and nutrition disorders
Uncommon: decreased appetite (0.7% vs. 0%)
Psychiatric disorders
Common: *depression (5.4% vs. 2%)*, hallucinations (1.3% vs. 0.7%)
Nervous system disorders
Very common: *headache (14.1% vs. 11.9%)*
Uncommon: cerebrovascular accident (0.7% vs. 0%)
Eye disorders
Common: conjunctivitis (2.7% vs. 0.7%)
Ear and labyrinth disorders
Common: vertigo (2.7% vs. 1.3%)
Cardiac disorders
Common: angina pectoris (1.3% vs. 0%)
Uncommon: myocardial infarction (0.7% vs. 0%)
Respiratory, thoracic and mediastinal disorders
Common: *rhinitis (3.4% vs. 0.7%)*
Gastrointestinal disorders
Common: flatulence (1.3% vs. 0%)
Skin and subcutaneous tissue disorders
Common: *dermatitis (2.0% vs. 0%)*
Uncommon: vesiculobullous rash (0.7% vs. 0%)
Musculoskeletal and connective tissue disorders
Common: *musculoskeletal pain (6.7% vs. 2.6%), neck pain (2.7% vs. 0%)*, arthritis (1.3% vs. 0.7%)
Renal and urinary disorders
Common: urinary urgency (1.3% vs. 0.7%)
General disorders and administration site conditions
Common: fever (2.7% vs. 1.3%), *malaise (2% vs. 0%)*

Adjunct Therapy

The list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies in patients receiving 1 mg/day Rasagiline (rasagiline group n=380, placebo group n=388). In parentheses is the adverse reaction incidence (% of patients) in rasagiline vs. placebo, respectively.

Adverse reactions with at least 2% difference over placebo are in *italics*.

Adverse reactions are ranked under headings of frequency using the following conventions: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000).

Neoplasms benign, malignant and unspecified
Uncommon: skin melanoma (0.5% vs. 0.3%)

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NEW MATERIAL
Material No.: 153118
Punch: Teva 0659
Size/mm.: 380x190
PCR No.: 933393

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Metabolism and nutrition disorders Common: decreased appetite (2.4% vs. 0.8%)
Psychiatric disorders Common: hallucinations (2.9% vs. 2.1%), abnormal dreams (2.1% vs. 0.8%) Uncommon: confusion (0.8% vs. 0.5%)
Nervous system disorders Very common: *dyskinesia (10.5% vs. 6.2%)* Common: dystonia (2.4% vs. 0.8%), carpal tunnel syndrome (1.3% vs. 0%), balance disorder (1.6% vs. 0.3%) Uncommon: cerebrovascular accident (0.5% vs. 0.3%)
Cardiac disorders Uncommon: angina pectoris (0.5% vs. 0%)
Vascular disorders Common: *orthostatic hypotension (3.9% vs. 0.8%)*
Gastrointestinal disorders Common: *abdominal pain (4.2% vs. 1.3%), constipation (4.2% vs. 2.1%), nausea and vomiting (8.4% vs. 6.2%), dry mouth (3.4% vs. 1.8%)*
Skin and subcutaneous tissue disorders Common: rash (1.1% vs. 0.3%)
Musculoskeletal and connective tissue disorders Common: arthralgia (2.4% vs. 2.1%), neck pain (1.3% vs. 0.5%)
Investigations Common: *decreased weight (4.5% vs. 1.5%)*
Injury, poisoning and procedural complications Common: fall (4.7% vs. 3.4%)

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.

Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/ tetracyclic antidepressants and MAO inhibitors. In the post-marketing period, cases of serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus have been reported by patients treated with antidepressants/SNRI concomitantly with Rasagiline.

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. There were no cases of serotonin syndrome in the Rasagiline clinical program in which 115 patients were exposed concomitantly to Rasagiline and tricyclics and 141 patients were exposed to Rasagiline and SSRIs/SNRIs.

In the post-marketing period, cases of elevated blood pressure, including rare cases of hypertensive crisis associated with ingestion of unknown amounts of tyramine-rich foods, have been reported in patients taking Rasagiline.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of impulse control disorders has been reported post-marketing with Rasagiline, which also included compulsions, obsessive thoughts and impulsive behaviour (see section 4.4).

With MAO inhibitors, there have been reports of drug interactions with the concomitant use of sympathomimetic medicinal products.
In post marketing period, there was one case of elevated blood pressure in a patient using ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking Rasagiline.

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes
Excessive daily sleepiness (hypersomnia, lethargy, sedation, sleep attacks, somnolence, and 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 medications, 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 medications, 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.

4.9 Overdose
Overdosage: Symptoms reported following overdose of Azilect® (Rasagiline mesilate) 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 events 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 undesirable reactions (including hypertension and postural hypotension) which resolved following treatment discontinuation. These symptoms may resemble those observed with non-selective MAO inhibitors.

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 Drug (Monoamine oxidase B inhibitor), 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 increase 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's not a MAO-B inhibitor.

Clinical studies:
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<0.00001; 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 end point, 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 1.
Plasma protein binding following a single oral dose of ^{14}C-labelled Rasagiline is approximately 60 to 70%.

Metabolism: 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.

Excretion: After oral administration of ^{14}C-labelled Rasagiline, elimination occurred primarily via urine (62.6%) and secondary 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 are linear with dose over the range of 0.5-2 mg. Its terminal half-life is 0.6-2 hours.

Characteristics in patients
Patients with 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.

Patients with 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 health subjects.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and reproduction toxicity.

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

Description of tablets
White to off-white, round, flat, beveled tablets, debossed with "GIL", and "1" underneath on one side and plain on the other side.

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

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Blisters:
Aluminum/aluminium blister pack x 7's in a box (physician's sample)
Aluminum/aluminum blister pack x 7's (box of 28's)

6.6 Special precautions for disposal
No special requirements.

6.7 Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
For suspected adverse drug reaction, report to the FDA:www.fda.gov.ph.
Patient is advised to seek medical attention immediately at the first sign of any adverse drug reaction that shall appear.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Teva Pharmaceuticals Industries Ltd,
Kfar Saba Plant, 18 Eli Hurvitz Street,
Industrial Zone,
Kfar Saba, 4410202,
Israel

For:
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Ottiliavej 9,
Valby, 2500, Denmark

Imported and distributed by:
METRO DRUG,INC.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna, Philippines

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