ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rasagiline Mylan 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains rasagiline tartrate corresponding to 1 mg rasagiline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, oblong (approximately 11.5 mm x 6 mm) biconvex tablets, debossed with 'R9SE' on one side and '1' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasagiline Mylan is indicated for the treatment of idiopathic Parkinson's disease (PD) 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

Rasagiline is administered orally, at a dose of 1 mg once daily with or without levodopa.

Elderly
No change in dose is required for elderly patients.

Hepatic impairment
Rasagiline use in patients with severe hepatic impairment is contraindicated (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).

Renal impairment
No change in dose is required for renal impairment.

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

Method of administration

For oral use.

Rasagiline 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

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.

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.

Since rasagiline potentiates the effects of levodopa, the adverse effects of levodopa may be increased and pre-existing dyskinesia exacerbated. Decreasing the dose of levodopa may ameliorate this side effect.

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 effects of hypotension due to existing gait issues.

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).

During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggests that Parkinson’s disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

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

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 (see section 4.3).

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).

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).

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).

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.

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 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of rasagiline. 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.

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

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.

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/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

For rasagiline no clinical data on exposed pregnancies is available. Animals studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding

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

No studies on the effects on the ability to drive and use machines have been performed.

Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that Rasagiline does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

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).

Tabulated list of adverse reactions

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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

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

Description of selected adverse reactions

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.

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 the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while 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).

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms reported following overdose of rasagiline in doses ranging from 3 mg to 100 mg included dysphoria, 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.

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 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 (Cmax) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%.

Food does not affect the Tmax of rasagiline, although Cmax 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.

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 are linear with dose over the range of 0.5-2 mg. Its terminal half-life is 0.6-2 hours.

Characteristics in patients

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 (CL_{cr} 50-80 ml/min) and moderate (CL_{cr} 30-49 ml/min) renal impairment were similar to healthy 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

6.1 List of excipients

Cellulose, microcrystalline
Tartaric acid
Maize starch
Starch, pregelatinised maize
Talc
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of

oPA/Al/PVC/Al. Blister packs of 7, 10, 28, 30, 100 or 112 tablets
PVC/PVDC/Al. Blister packs of 7, 10, 28, 30, 100 or 112 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117, Allée des Parcs,
69800 Saint-Priest
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1090/001 (7 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/002 (10 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/003 (28 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/004 (30 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/005 (100 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/006 (112 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/007 (7 tablets - PVC/PVDC/alu)
EU/1/16/1090/008 (10 tablets - PVC/PVDC/alu)
EU/1/16/1090/009 (28 tablets - PVC/PVDC/alu)
EU/1/16/1090/010 (30 tablets - PVC/PVDC/alu)
EU/1/16/1090/011 (100 tablets - PVC/PVDC/alu)
EU/1/16/1090/012 (112 tablets - PVC/PVDC/alu)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Mylan Hungary Kft
Mylan utca 1
H-2900 Komárom
Hungary

Synthon Hispania S.L.
C/ Castelló no1, Pol. Las Salinas
08830, Sant Boi de Llobregat, Barcelona
Spain

Synthon s.r.o
Brněnská 32/čp. 597
678 01 Blansko
Czech Republic

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Rasagiline Mylan 1 mg tablets
rasagiline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains rasagiline tartrate corresponding to 1 mg rasagiline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

7 tablets
10 tablets
28 tablets
30 tablets
100 tablets
112 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117, Allée des Parcs
69800 Saint-Priest
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1090/001 (7 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/002 (10 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/003 (28 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/004 (30 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/005 (100 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/006 (112 tablets - oPA/alu/PVC/alu)
EU/1/16/1090/007 (7 tablets - PVC/PVDC/alu)
EU/1/16/1090/008 (10 tablets - PVC/PVDC/alu)
EU/1/16/1090/009 (28 tablets - PVC/PVDC/alu)
EU/1/16/1090/010 (30 tablets - PVC/PVDC/alu)
EU/1/16/1090/011 (100 tablets - PVC/PVDC/alu)
EU/1/16/1090/012 (112 tablets - PVC/PVDC/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasagiline Mylan

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rasagiline Mylan1 mg tablets
rasagiline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan S.A.S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rasagiline Mylan 1 mg tablets
rasagiline

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rasagiline Mylan is and what it is used for

Rasagiline Mylan is used for the treatment of Parkinson's disease. It can be used together with or without levodopa (another medicine that is used to treat Parkinson's disease).

With Parkinson's disease, there is a loss of cells that produce dopamine in the brain. Dopamine is a chemical in the brain involved in movement control. Rasagiline Mylan helps to increase and sustain levels of dopamine in the brain.

2. What you need to know before you take Rasagiline Mylan

Do not take Rasagiline Mylan:
- if you are allergic to rasagiline or any of the other ingredients of this medicine (listed in section 6).
- if you have severe liver problems.

Do not take the following medicines while taking Rasagaline Mylan:
- monoamine oxidase (MAO) inhibitors (e.g. for treatment of depression or Parkinson's disease, or used for any other indication), including medicinal and natural products without prescription e.g. St. John's Wort.
- pethidine (a strong pain killer).

You must wait at least 14 days after stopping Rasagiline Mylan treatment and starting treatment with MAO inhibitors or pethidine.

Warnings and precautions
Talk to your doctor before taking Rasagiline Mylan.
- if you have **mild to moderate liver problems**
- if you have any suspicious **skin changes**.

Children and adolescents
Rasagiline Mylan is not recommended for use under the age of 18.

Other medicines and Rasagiline Mylan
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without prescription or if you are smoking or intend to stop smoking.

Ask your doctor for advice before taking any of the following medicines together with Rasagiline Mylan:
Certain antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or tetracyclic antidepressants)
the antibiotic ciprofloxacin used against infections
the cough suppressant dextromethorphan
sympathomimetics such as those present in eye drops, nasal and oral decongestants and cold medicine containing ephedrine or pseudoephedrine

The use of Rasagiline Mylan together with the antidepressants containing fluoxetine or fluvoxamine should be avoided.

If you are starting treatment with Rasagiline Mylan, you should wait at least 5 weeks after stopping fluoxetine treatment.

If you are starting treatment with fluoxetine or fluvoxamine, you should wait at least 14 days after stopping Rasagiline Mylan treatment.

Tell your doctor if you or your family/carer notices that you are developing unusual behaviours where you cannot resist the impulse, urges or cravings to carry out certain harmful or detrimental activities to yourself or others. These are called impulse control disorders. In patients taking Rasagiline Mylan and/or other medications used to treat Parkinson's disease, behaviours such as compulsions, obsessive thoughts, addictive gambling, excessive spending, impulsive behaviour and an abnormally high sex drive or an increase in sexual thoughts or feelings have been observed. Your doctor may need to adjust or stop your dose.

Rasagiline Mylan with food and drink
Rasagiline Mylan may be taken with or without food.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. Ask your doctor for advice prior to driving or using machines.

3. How to take Rasagiline Mylan

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 1 tablet of 1 mg taken by mouth once daily. Rasagiline Mylan may be taken with or without food.

If you take more Rasagiline Mylan than you should
If you think that you may have taken too many Rasagiline Mylan tablets, contact your doctor or pharmacist immediately. Take the Rasagiline Mylan carton with you to show the doctor or pharmacist.

If you forget to take Rasagiline Mylan

Do not take a double dose to make up for a forgotten dose. Take the next dose normally, when it is time to take it.

If you stop taking Rasagiline Mylan
Do not stop taking Rasagiline Mylan without first talking to your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported in placebo controlled clinical trials:

The frequency of possible side effects listed below is defined using the following convention:
- Very common (may affect more than 1 in 10 people)
- Common (may affect up to 1 in 10 people)
- Uncommon (may affect up to 1 in 100 people)
- Rare (may affect up to 1 in 1,000 people)
- Very rare (may affect up to 1 in 10,000 people)
- Not known (frequency cannot be estimated from the available data)

Very common
- abnormal movements (dyskinesia)
- headache

Common
- abdominal pain
- fall
- allergy
- fever
- flu (influenza)
- general feeling of being unwell (malaise)
- neck pain
- chest pain (angina pectoris)
- low blood pressure when rising to a standing position with symptoms like dizziness/light
- headedness (orthostatic hypotension)
- decreased appetite
- constipation
- dry mouth
- nausea and vomiting
- flatulence
- abnormal results of blood tests (leucopenia)
- joint pain (arthralgia)
- musculoskeletal pain
- joint inflammation (arthritis)
- numbness and muscle weakness of the hand (carpal tunnel syndrome)
- decreased weight
- abnormal dreams
- difficulty in muscular coordination (balance disorder)
- depression
- dizziness (vertigo)
- prolonged muscle contractions (dystonia)
- runny nose (rhinitis)
- irritation of the skin (dermatitis)
- rash
- bloodshot eyes (conjunctivitis)
- urinary urgency

Uncommon
- stroke (cerebrovascular accident)
- heart attack (myocardial infarction)
- blistering rash (vesiculobullous rash)

In addition, skin cancer was reported in around 1% of patients in the placebo controlled clinical trials. Nevertheless, scientific evidence suggests that Parkinson's disease, and not any medicine in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). You should speak with your doctor about any suspicious skin changes.

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.

There have been cases of patients who, while taking one or more medications for the treatment of Parkinson's disease, were unable to resist the impulse, drive or temptation to perform an action that could be harmful to themselves or others. These are called impulse control disorders. In patients taking rasagiline and/or other medications used to treat Parkinson's disease, the following have been observed:
- Obsessive thoughts or impulsive behaviour.
- Strong impulse to gamble excessively despite serious personal or family consequences.
- Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.
- Uncontrollable excessive shopping or spending.

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rasagiline Mylan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasagiline Mylan contains
- The active substance is rasagiline. Each tablet contains rasagiline tartrate corresponding to 1 mg rasagiline.
- The other ingredients are microcrystalline cellulose, tartric acid, maize starch, pregelatinized maize starch, talc, stearic acid.

What Rasagiline Mylan looks like and contents of the pack
Rasagiline tablets are presented as white to off-white, oblong (approximately 11.5 mm x 6 mm) biconvex tablets, debossed with 'R9SE' on one side and '1' on the other side.

The tablets are available in blister packs of 7, 10, 28, 30, 100 and 112 tablets.

Not all pack sizes may be marketed.

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