Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rasagiline Accord 1mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg rasagiline (as rasagiline tartrate). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round, flat, bevelled tablets (6.5 mm).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rasagiline Accord 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. It may be taken with or without food.
Elderly: No change in dose is required for elderly patients.

Paediatric population: Rasagiline Accord 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 (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).

Patients 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 see 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.
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 (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 interactions

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.

*Invitro*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.

*Invitro*studies showed that rasagiline at a concentration of 1 µg/ml (equivalent to a level that is 160 times the average Cmax ~ 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/rasagilineinteraction:*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

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.

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 Accord does not affect them adversely.

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

Neoplasms benign, malignant and unspecified 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%)

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

4.9 Overdose

Overdosage: Symptoms reported following overdose of Azilect 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.

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 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<0.0001; 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 (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%.

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 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
Patients with hepatic impairment: In subjects with mild hepatic impairment, AUC and Cmax were increased by 80% and 38%, respectively. In subjects with moderate hepatic impairment, AUC and Cmax were increased by 568% and 83%, respectively (see section 4.4).

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 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 *invivo*and in several *invitro*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
Maizestarch
Starch,Pregalatinised(frommaize)
Talc
SodiumStearylFumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-Aluminium blisters, Clear PVC/PE/PVdC-aluminium blister Pack sizes of 7, 10 , 28, 30, 60,100, 112 tablets

HDPE tablet container with PP child resistant screw cap containing desiccant (silicia gel) Pack sizes of 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/174/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th November 2015

10 DATE OF REVISION OF THE TEXT

May 2019