

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT FOR HUMAN USE

ETKINIA® 1 mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMBINATION

Active substance:

Each tablet contains 1.56 mg rasagiline mesylate equivalent to 1 mg rasagiline as active substance.

Excipients:

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet

White, round, flat tablets.

4. CLINICAL FEATURES

4.1 Therapeutic indications

ETKINIA® is indicated for the treatment of Parkinson's disease.

4.2 Posology and route of administration

Posology/frequency and duration of administration:

Rasagiline is given orally at a dose of 1 mg once daily.

Method of administration:

It can be taken with food or alone. It should be taken with a glass of water.

Additional information on special populations:

Renal impairment:

No change in dose is necessary in patients with renal impairment.

Hepatic impairment:

Rasagiline is contraindicated in patients with severe hepatic impairment (see section 4.3.).

The use of rasagiline should be avoided in patients with moderate hepatic impairment. Caution should be exercised when initiating treatment with rasagiline in patients with mild hepatic impairment. In patients who progress from mild hepatic impairment to moderate hepatic impairment, rasagiline should be discontinued (see sections 4.4. and 5.2.).

Pediatric population:

Due to the lack of adequate data on safety and efficacy, rasagiline is not recommended for use in children and adolescents under 18 years of age.

Geriatric population:

No dose modification is necessary for elderly patients (see section 5.2.).

4.3 Contraindications

ETKINIA® is contraindicated in the following cases:

- Hypersensitivity to the active substance or any of the excipients (see section 6.1.).
- It is contraindicated in combination with other monoamino oxidase (MAO) inhibitors

(including over-the-counter medicinal and natural products, e.g. St. John's Wort) and pethidine (see section 4.5). At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine.

- In patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Concomitant use of Rasajilin and other medicinal products

Concomitant use of rasagiline with fluoxetine or fluvoxamine should be avoided (see section 4.5.). At least five weeks should elapse between stopping fluoxetine and starting treatment with rasagiline. At least 14 days should elapse between stopping rasagiline and starting treatment with fluoxetine or fluvoxamine.

Concomitant use of rasagiline and dextromethorphan or sympathomimetics (such as nasal and oral decongestants containing ephedrine or pseudoephedrine or cold medicines) is not recommended (see section 4.5).

Concomitant use of rasagiline and levodopa

Because rasagiline increases the effect of levodopa, there may be an increase in levodopa-related adverse effects and pre-existing dyskinesia may be exacerbated. Reducing the dose of levodopa may improve this side effect.

There have been reports of hypotensive effects when rasagiline is taken with levodopa. People with Parkinson's disease are particularly susceptible to adverse effects from hypotension due to difficulty in walking.

Dopaminergic effects

Episodes of excessive daytime sleepiness (ODS) and sudden onset of sleep (AUB)

Rasagiline may cause daytime sleepiness, somnolence and occasional falling asleep during activities of daily living when used in combination with other dopaminergic drugs. Patients should be informed about this and advised to be careful when driving or operating machinery during rasagiline treatment. Patients experiencing drowsiness and/or sudden sleep attacks should avoid driving or operating machinery (see section 4.7).

Impulse control disorders

Impulse control disorders may occur in patients treated with dopamine agonists and/or dopaminergic drugs. There have been similar post-marketing reports of impulse control disorders for rasagiline. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be aware that compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behavior and compulsive money should be informed about behavioral symptoms of impulse control disorders, including spending or shopping.

Melanoma

A retrospective cohort study suggested a possible increased risk of melanoma with rasagiline use, particularly in patients with longer exposure to rasagiline and/or a higher cumulative dose of rasagiline. Any suspicious skin lesion should be evaluated by a qualified physician. Patients should therefore be advised to seek medical advice if a new or changing skin lesion is detected.

Liver failure

Caution is required when initiating rasagiline treatment in patients with mild hepatic impairment. The use of rasagiline should be avoided in patients with moderate hepatic impairment. Rasagiline should be discontinued in patients with progression from mild hepatic impairment to moderate hepatic impairment (see section 5.2.).

4.5 Interactions with other medicinal products and other forms of interaction

MAO inhibitors

The concomitant use of rasagiline with other MAO inhibitors (including over-the-counter medicinal and natural products, e.g. St. John's Wort) is contraindicated, as there may be a risk of non-selective MAO inhibition leading to hypertensive crises (see section 4.3.).

Pethidine

Serious side effects have been reported in the concomitant use of MAO inhibitors, including other selective MAO-B inhibitors, and pethidine. Concomitant use of rasagiline and pethidine is contraindicated (see section 4.3.).

Sympathomimetics

There have been reports of drug interactions in the concomitant use of MAO inhibitors and sympathomimetic drugs. Due to the MAO inhibitory effect of rasagiline, concomitant administration of rasagiline and sympathomimetics (such as cold medicines containing ephedrine or pseudoephedrine and sympathomimetics contained in nasal and oral decongestants) is not recommended (see section 4.4.).

Dextromethorphan

There have been reports of drug interactions with concomitant use of dextromethorphan and non-selective MAO inhibitors. Due to the MAO inhibitory effect of rasagiline, concomitant administration of rasagiline and dextromethorphan is not recommended (see section 4.4.).

SNRIs, SSRIs, tricyclic and tetracyclic antidepressants

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

See section 4.8 for the concomitant use of rasagiline and selective serotonin reuptake inhibitors (SSRIs)/selective serotonin-norepinephrine reuptake inhibitors (SNRIs) in clinical trials.

Concurrent use of SSRIs, SNRIs, tricyclic, tetracyclic antidepressants and MAO inhibitors serious adverse effects have been reported in its use. Due to the MAO inhibitory effect of rasagiline, antidepressants should be used with caution.

Agents affecting CYP1A2 activity

In vitro metabolism studies have shown that the main enzyme responsible for the

metabolism of rasagiline is P4501A2 (CYP1A2).

CYP1A2 inhibitors

Co-administration of rasagiline and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC (area under the curve) of rasagiline by 83%. Co-administration of rasagiline and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either product. Strong CYP1A2 inhibitors can alter plasma levels of rasagiline and should therefore be given with caution.

CYP1A2 inducers

In smoking patients, there is a risk of decreased plasma levels of rasagiline due to induction of the metabolizing enzyme CYP1A2.

Other cytochrome P450 isoenzymes

In vitro studies have shown that rasagiline does not inhibit cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A) at a concentration of 1 mcg/ml (equivalent to 160 times the mean C_{max} ~ 5.9-8.5 ng/mL in Parkinson's disease patients after a 1 mg multiple dose of rasagiline). These results indicate that therapeutic concentrations of rasagiline are not expected to cause clinically relevant interactions with substrates of these enzymes (see section 5.3.).

Levodopa and other Parkinson's disease treatment products

In Parkinson's disease patients receiving chronic levodopa as adjuvant therapy, levodopa treatment had no clinically significant effect on the clearance of rasagiline.

Concomitant administration of rasagiline and entacapone increased the oral clearance of rasagiline by 28%. Tyramine/rasagiline interaction

Tyramine/rasagiline interaction

The results of five studies with tyramine (in volunteers and patients with Parkinson's disease), together with the results of home monitoring of blood pressure after meals (464 patients treated with rasagiline 0.5 or 1 mg daily or placebo as adjunctive therapy to levodopa without tyramine restriction for six months) and the absence of any reports of tyramine/rasagiline interactions in clinical trials without tyramine restriction, indicate that rasagiline can be used safely without dietary tyramine restrictions.

4.6 Pregnancy and lactation G

General advice

Pregnancy category: C.

Women of childbearing potential / Birth control (Contraception) Patients should inform their doctor if they become pregnant or plan to become pregnant during treatment with ETKINIA.®

Pregnancy period

There are no clinical data on the use of rasagiline in pregnancy. Animal studies do not indicate direct or indirect harmful effects in relation to pregnancy, embryonal/fetal development, parturition or postnatal development. (see section 5.3.). The potential risk to humans is not known. The benefits of drug treatment during pregnancy should be weighed against the potential risk to the fetus. AZILECT should not be used during pregnancy unless absolutely necessary.

Lactation period

According to experimental data, rasagiline inhibits prolactin release and may therefore inhibit breastfeeding. It is not known whether rasagiline is excreted in breast milk. It should not be given during breastfeeding.

Reproductive ability / Fertility

No human data on the effect of rasagiline on fertility are available.

4.7 Effects on driving and use of machinery

Rasagiline may significantly affect the ability to drive and use machines in patients experiencing drowsiness or sudden sleep attacks.

Patients should be warned to be careful when operating dangerous machinery, including motor vehicles, until they are sufficiently sure that rasagiline is not adversely affecting them.

Patients treated with rasagiline who experience drowsiness and/or sudden episodes of sleep should be advised to avoid driving or activities that carry a risk of serious injury or death to themselves or others (e.g. operating machinery) until they have gained sufficient experience with rasagiline and other dopaminergic drugs to avoid adverse effects on mental and/or motor performance.

Patients should not drive or participate in potentially hazardous activities if, at any time during their treatment, drowsiness or episodes of falling asleep during activities of daily living (e.g. watching television, traveling by car, etc.) increase.

Patients should not drive, operate machinery or work at height during treatment if they have experienced drowsiness and/or sudden sleep attacks without any warning before the use of rasagiline.

Patients should be warned about the possible additive effect of concomitant use of rasagiline with sedative drugs, alcohol or other central nervous system depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or drugs that increase plasma levels (e.g. ciprofloxacin) (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse effects in clinical trials in people with Parkinson's disease are as follows:

They included headache, depression, vertigo and influenza (influenza and rhinitis) in monotherapy; dyskinesia, orthostatic hypotension, falls, abdominal pain, nausea and vomiting and dry mouth in adjuvant treatment with levodopa; musculoskeletal pain, back and neck pain and arthralgia in both treatment regimens. These adverse effects were not associated with an increased rate of discontinuation of treatment.

Tabulated list of undesirable effects

Undesirable effects are given below as Tables 1 and 2 in order of system organ class and frequency: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), unknown (cannot be estimated from available data).

Monotherapy

The following list includes adverse effects reported with a higher incidence in placebo-controlled studies in patients receiving 1 mg rasagiline daily.

System Organ Class	Very common	Widespread	Uncommon	Unknown
Infection and infestations		Influenza		
Benign, malignant and unspecified neoplasms (including cysts and polyps)		Skin carcinoma		
Blood and lymph system diseases		Leukopenia		
Immune system diseases		Allergy		
Metabolism and nutrition diseases			Decreased appetite	
Psychiatric illnesses		Depression Hallucinations		Impulse control disorders*
Nervous system diseases	Headache		Cerebrovascular damage	Serotonin syndrome*, excessive daytime sleepiness (DOS) and sudden onset of sleep (AUB) episodes

Eye diseases		Conjunctivitis		
Ear and inner ear diseases		Vertigo		
Cardiac diseases		Angina pectoris	Myocardial infarction	
Vascular diseases				Hypertension*
Respiratory, chest disorders and mediastinal diseases		Rhinitis		
Gastrointestinal diseases		Flatulans		
Skin and subcutaneous tissue diseases		Dermatitis	Vesiculobullous Rash	
Musculoskeletal disorders, connective tissue and bone diseases		Musculoskeletal pain, neck pain, arthritis		
Kidney and urinary tract diseases		Sudden urine compression		
On general disorders and the region of application Diseases		Fever, malaise		

* For undesirable effects, see "Description of selected adverse reactions".

Adjuvant Treatment

The following list includes adverse effects reported with a higher incidence in placebo-controlled studies in patients receiving 1 mg rasagiline daily.

System Organ Class	Very common	Widespread	Uncommon	Unknown
Benign, malignant and unspecified neoplasms (including cysts and polyps)			Skin melanoma	
Metabolism and nutritional diseases		Decreased appetite		
Psychiatric Diseases		Hallucinations*, Abnormal dreams	Confusion	Impulse control disorders*
Nervous system diseases	Dyskinesia	Dystonia, Carpal tunnel syndrome, Balance disorders	Cerebrovascular damage	Serotonin syndrome*, excessive daytime sleepiness (ODS) and sudden onset of sleep (AUB) episodes
Cardiac Diseases			Angina pectoris	
Vascular diseases		Orthostatic hypotension*		Hypertension*
Gastrointestinal diseases		Abdominal pain, constipation, nausea and vomiting, Dry mouth		
Skin and subcutaneous tissue diseases		Rash		
Musculoskeletal disorders, ligament tissue and bone diseases		Arthralgia, Neck pain		
Research		Weight loss		
General disorders and practice diseases related to the region		Falling		

* For undesirable effects, see "Description of selected adverse reactions".

Description of selected adverse reactions

Orthostatic hypotension

In blinded, placebo-controlled studies, severe orthostatic hypotension was reported in one patient (0.3%) in the rasagiline arm (additional studies) and the same effect was not observed in the placebo arm. In addition, clinical study data suggest that orthostatic hypotension frequently occurs in the first two months of rasagiline treatment and tends to decrease over time.

Hypertension

Rasagiline selectively inhibits the MAO-B enzyme and at the indicated dose (1 mg/day) is not associated with increased tyramine sensitivity. In blinded, placebo-controlled studies (monotherapy and adjuvant treatment), no patients in the rasagiline arm reported severe hypertension. In the postmarketing period, elevations in blood pressure have been reported in patients receiving rasagiline, including rare cases of severe hypertensive crisis associated with the ingestion of unknown amounts of tyramine-rich foods. In the postmarketing period, hypertension was reported in one patient who also used the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking rasagiline.

Impulse control disorders

One case of hypersexuality was reported in a placebo-controlled monotherapy study. In postmarketing use, the following effects have been reported with unknown frequency: Compulsions, compulsive shopping, dermatomania, dopamine dysregulation syndrome, impulse control disorder, impulsive behavior, kleptomania, theft, obsessive thoughts, obsessive-compulsive disorder, stereotypy, gambling, pathological gambling, increased libido, hypersexuality, psychosexual disorder, inappropriate sexual behavior. Half of the reported cases of DID were considered serious. Of the reported cases, only one case had not improved at the time of reporting.

Episodes of excessive daytime sleepiness (ODS) and sudden onset of sleep (AUB)

Excessive daytime sleepiness (hypersomnia, lethargy, sedation, sleep attacks, somnolence, sudden onset of sleep) may occur in patients treated with dopamine agonists and/or other dopaminergic drugs. A similar pattern of excessive daytime sleepiness has been reported with rasagiline in the postmarketing period.

Cases of falling asleep during activities of daily living have been reported in patients treated with rasagiline and other dopaminergic drugs. Although some of these patients reported drowsiness while taking rasagiline and other dopaminergic drugs, others felt that there were no warning signs such as excessive sleepiness and thought that they became aware of it immediately after the event. Some of these events were reported at least 1 year after the start of treatment.

Hallucinations

Parkinson's disease is associated with symptoms of hallucinations and confusion. In postmarketing experience, these symptoms have also been observed in Parkinson's patients

treated with rasagiline.

Serotonin syndrome

The concomitant use of fluoxetine or fluvoxamine with rasagiline was not allowed in clinical trials with rasagiline, but the following antidepressants and doses were allowed in rasagiline studies Amitriptyline ≤ 50 mg/day, trazodone ≤ 100 mg/day, citalopram ≤ 20 mg/day, sertraline ≤ 100 mg/day and paroxetine ≤ 30 mg/day (see section 4.5).

In the postmarketing period, cases of potentially life-threatening serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonia have been reported in patients taking rasagiline concomitantly with antidepressants, meperidine, tramadol, methadone or propoxyphene.

Malignant melanoma

In placebo-controlled clinical trials, the incidence of skin melanoma was 2/380 (0.5%) in the levodopa and 1 mg rasagiline treatment group and 1/388 (0.3%) in the placebo group. Additional cases of malignant melanoma were reported in the post-marketing period. These cases were considered serious in all reports.

Reporting of side effects

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization 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.

4.9 Overdose and treatment

Overdose: Symptoms reported after overdose of ETKINIA[®] at doses ranging from 3 mg to 100 mg include hypomania, hypertensive crisis and serotonin syndrome. Overdose may be associated with significant inhibition of MAO-A and MAO-B. Healthy volunteers in a single dose study received 20 mg daily and healthy volunteers in a ten-day study received 10 mg daily. Adverse effects were mild or moderate and not associated with rasagiline treatment. In a dose titration study in patients on chronic levodopa therapy treated with rasagiline 10 mg daily, there were reports of cardiovascular adverse effects (including hypertension and postural hypotension) that resolved after discontinuation of treatment. These symptoms may be similar to those observed with non-selective MAO inhibitors.

There is no specific antidote. In case of overdose, patients should be monitored and supportive treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinsonian Drugs, Monoaminoxidase -B inhibitors
ATC code: N04BD02

Mechanism of action:

Rasagiline has been shown to be a potent and irreversible MAO-B selective inhibitor that can cause an increase in extracellular dopamine levels in the striatum. The beneficial effects of rasagiline in models of dopaminergic motor dysfunction are likely mediated through elevated dopamine levels and subsequent increased dopaminergic activity.

1-Aminoindan is an active parent metabolite and is not an MAO-B inhibitor.

Clinical trials:

Monotherapy:

In Study I, 404 patients were randomized to receive placebo (138 patients), rasagiline 1 mg daily (134 patients) or rasagiline 2 mg daily (132 patients) and were treated for 26 weeks. There was no active comparator agent.

In this study, the primary efficacy measure was change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS, parts I-III) total score. The difference in mean change from baseline to Week 26/end of study (LOCF, Last Observation Carried Forward) was statistically significant (UPDRS, parts I-III: Rasagiline 1 mg vs placebo -4.2, 95% CI [-5.7, -2.7]; $p < 0.0001$; rasagiline 2 mg vs placebo - 3.6, 95% CI [-5.0, -2.1]; $p < 0.0001$, UPDRS Motor, part II: Rasagiline 1 mg vs placebo -2.7, 95% CI [-3.87, -1.55], $p < 0.0001$; rasagiline 2 mg vs placebo -1.68, 95% CI [-2.85, -0.51], $p = 0.005$). Moderate but proven effect in this patient population with mild disease. It has a significant and beneficial effect on quality of life (assessed by the PD-QUALIF scale).

Adjuvant Treatment

In Study II, patients were randomized to receive placebo (229 patients), rasagiline 1 mg daily (231 patients), or entacapone 200 mg COMT inhibitor in combination with scheduled doses of levodopa (LD)/decarboxylase inhibitor and treated for 18 weeks. In Study III, patients were randomized to receive placebo (159 patients), rasagiline 0.5 mg daily (164 patients), or rasagiline 1 mg daily (149 patients) and were treated for 26 weeks.

In both studies, the primary measure of efficacy was the change in the mean time spent in the "OFF" state throughout the day from baseline to treatment (determined from "24-hour" home diaries completed on the 3 days before each of the assessment visits).

In Study II, the mean change in time spent in the "OFF" state compared with placebo was -0.78 hours, 95% CI [-1.18, -0.39] ($p < 0.0001$). The mean total daily reduction in OFF time of 0.8 hours in the entacapone group was similar to that observed in the 1 mg rasagiline group. The mean change compared to placebo in Study III was -0.94 hours (95% CI [-1.2, -0.41], $p < 0.0001$). There was also a statistically significant improvement with the rasagiline 0.5 mg group compared to placebo, but the magnitude of the improvement was lower. The robustness of the results for the primary efficacy endpoint was confirmed in a number of

additional statistical models and shown in three cohorts (ITT per protocol and complement).

Secondary measures of efficacy included global assessments of improvement by the examiner (Activities of Daily Living (ADL) subscale during OFF and UPDRS motor scores during ON). Rasajiline showed statistically significant benefit compared to placebo.

Study IV was an 18-week double-blind, randomized, placebo-controlled, parallel-group, double-blind, randomized, placebo-controlled study investigating ETKINIA[®] 1 mg as adjunctive therapy to dopamine agonists without concomitant levodopa treatment. Patients were treated for ≥ 30 days with stable doses of dopamine agonists (ropinirole, mean 8 mg/day or pramipexole, mean 1.5 mg/day) at doses that were stable but not sufficient to control symptoms of Parkinson's disease.

In Study IV, 321 patients were randomly assigned to receive placebo (162 patients) or AZILECT 1 mg/day (159 patients) and underwent a post-baseline evaluation. The mean duration of Parkinson's disease was approximately 2 years (range: 0.1 to 14.5 years).

The primary efficacy measure was change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) [mental activity (Part I) + activities of daily living (ADL) (Part II) + motor function (Part III)] total score.

In Study IV, ETKINIA[®] 1 mg was superior to placebo on the primary efficacy measure.

Change in Total UPDRS Score in Study IV:

	Initial score	Change score from baseline to outcome*	p-value versus placebo
Placebo	29,8	-1,2	—
ETKINIA [®] 1 mg	32,1	-3,6	0,012

*A negative change from baseline indicates an increase in UPDRS.

The secondary outcome assessment of the individual subscales of the UPDRS shows that the UPDRS Part III motor subscale is predominantly responsible for the overall effect of AZILECT on the UPDRS score.

Secondary Effectiveness Measures in Study IV:

	Start (score)	Change score from baseline to outcome*
UPDRS Part II ADL (Activities of Daily Living) subscale score		
Placebo	7,9	0,4
AZILECT 1 mg	8,6	-0,3
UPDRS Part III Motor subscale score		
Placebo	20,4	-1,2
AZILECT 1 mg	22,2	-3,7

5.2 Pharmacokinetic properties

General features:

The pharmacokinetic profile is similar in men and women.

Absorption

Rasagiline is rapidly absorbed and reaches a peak plasma concentration (C_{max}) in about 0.5 hours. The absolute bioavailability of a single dose of rasagiline is approximately 36%. Although food does not affect the T_{max} of rasagiline, the C_{max} and area under the curve (AUC) values decrease by approximately 60% and 20%, respectively, when rasagiline is taken with a high-fat meal. Since the AUC is not significantly affected, rasagiline can be taken alone or with meals.

Distribution:

The mean volume of distribution after a single i.v. dose of rasagiline is 243 liters: ¹⁴After a single oral dose of rasagiline labeled with C, plasma protein binding is approximately 60% to 70%.

Biotransformation:

Rasagiline undergoes near complete biotransformation in the liver. Rasagiline metabolism proceeds through two main pathways: N-dealkylation and/or hydroxyalkylation to provide 1-aminoindan, 3-hydroxy-N-propargyl-1-aminoindan and 3-hydroxy-1-aminoindan. According to *in vitro* experiments, both routes of action of rasagiline metabolism are dependent on the cytochrome P450 system and CYP1A2 is the main isoenzyme involved in rasagiline metabolism. Conjugation of rasagiline and its metabolites to form glucuronates has also been shown to be the major route of elimination. Ex vivo and in vitro experiments have shown that rasagiline is not an inhibitor or inducer of major CYP450 enzymes (see section 4.5).

Elimination:

After oral administration of ¹⁴C-labeled rasagiline, elimination occurred primarily in the urine (62.6%) and secondarily in the faeces (21.8%), with a total of 84.4% of the dose eliminated over a 38-day period. Less than 1% of rasagiline was excreted unchanged in the urine.

Linearity/nonlinearity:

The pharmacokinetics of rasagiline is linear in the dose range of 0.5-2 mg. The half-life at termination is 0.6-2 hours.

Characteristic features in patients:

Patients with liver disorders:

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

Patients with kidney disorders:

In patients with mild (creatinine clearance 50-80 mL/minute) and moderate (creatinine clearance 30-49 mL/minute) renal impairment, the pharmacokinetic properties of rasagiline are similar to those in healthy subjects.

Geriatric patients:

Age has an insignificant effect on the pharmacokinetic properties of rasagiline (see section 4.2).

5.3 Preclinical safety data

Preclinical data based on conventional studies of safety pharmacology (repeated dose toxicity, genotoxicity, carcinogenicity, reproduction and development) have shown that no specific hazard to humans has emerged.

Rasagiline has not shown genotoxic potential in various *in vitro* and *in vivo* systems using bacteria or hepatocytes. Rasagiline, in the presence of the active metabolite, induced an increase in chromosomal abnormalities at extreme cytotoxic concentrations that are not achievable under conditions of clinical use.

In rats systemically exposed to rasagiline (84-339 times the expected plasma levels in humans at a dose of 1 mg daily), rasagiline did not cause carcinogenic effects. An increased incidence of combined bronchial/alveolar adenoma and/or carcinoma was observed in mice exposed to systemic administration (144-213 times the plasma levels expected in humans at a dose of 1 mg daily).

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Pregelatinized starch
Talc
Mannitol (E421)
Corn starch
Colloidal silicon dioxide
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25 °C in the original packaging.

6.5 Nature and content of the packaging

Packaged in Alu/Alu - Aluminum foil blister containing 30 and 100 tablets.

6.6 Disposal of residues of medicinal products for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging and Packaging Waste".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

248/52

9. DATE OF FIRST LICENSE/RENEWAL OF THE LICENSE

15/02/2013

10. DATE OF REVISION OF THE TEXT

Not applicable