PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. Name of the medicine

RAZAGIN™ (1 mg) tablets

2. Qualitative and quantitative composition

Each tablet contains 1 mg rasagiline (as rasagiline tartrate).

Sugar free

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets

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

4. Clinical particulars

4.1 Therapeutic indications

RAZAGIN 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

The recommended dose of RAZAGIN is 1 mg (1 tablet) once daily, with or without levodopa.

Elderly:

No change in dose is required for elderly patients.

Children and adolescents (< 18 years):

RAZAGIN is not recommended as safety and efficacy have not been established in this population.

Patients with hepatic impairment:

RAZAGIN use in patients with moderate or severe hepatic impairment is contraindicated (see section 4.3). Caution should be used when initiating treatment with RAZAGIN in patients with mild hepatic insufficiency. In case patients progress from mild to moderate hepatic impairment RAZAGIN should be stopped (see section 4.4).

Patients with renal impairment:

No change in dose is required for renal impairment.

Method of administration

For oral use.

RAZAGIN may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to rasagiline or to any of the excipients of RAZAGIN, listed in section 6.1.
- Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including products without prescription e.g. St. John's Wort) or pethidine (see section 4.5). At least 14 days must elapse between discontinuation of RAZAGIN and initiation of treatment with MAO inhibitors or pethidine.
- Moderate or severe hepatic impairment (Child Pugh B and C).

4.4 Special warnings and precautions for use

Concomitant use of RAZAGIN with other medicines

The concomitant use of RAZAGIN 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 RAZAGIN. At least 14 days should elapse between discontinuation of RAZAGIN and initiation of treatment with fluoxetine or fluvoxamine.

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

Concomitant use of RAZAGIN and levodopa

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

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

Dopaminergic effects

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

Rasagiline as in RAZAGIN may cause daytime drowsiness, somnolence, and less frequently (especially if used with other dopaminergic medicines) falling asleep during activities of daily living. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with RAZAGIN. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section 4.7).

Impulse control disorders (ICDs)

ICDs can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Similar reports of ICDs have also been received post-marketing with rasagiline (contained in RAZAGIN). 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 as in RAZAGIN, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

Melanoma

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

Hepatic impairment

Caution should be used when initiating treatment with RAZAGIN in patients with mild hepatic impairment. RAZAGIN use in patients with moderate or severe hepatic impairment is contraindicated. In case patients progress from mild to moderate hepatic impairment, RAZAGIN should be stopped (see section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

MAO Inhibitors

There are a number of known interactions between non-selective MAO inhibitors and other medicines.

RAZAGIN should not be administered along with other MAO inhibitors (including medicines and natural products obtained without prescription e.g. St. John's Wort) as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crises (see section 4.3).

Pethidine

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

Sympathomimetics

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

Dextromethorphan

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

SNRI/SSRI/tri- and tetracyclic antidepressants

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

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors as well as with another selective MAO-B inhibitor. Therefore, in view of the MAO inhibitory activity of rasagiline as in RAZAGIN, antidepressants should be administered with caution.

Medicines that affect CYP1A2 activity

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

CYP1A2 inhibitors

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

CYP1A2 inducers

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

Other cytochrome P450 isoenzymes

In vitro studies showed that rasagiline as in RAZAGIN 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 as in RAZAGIN's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

Levodopa and other Parkinson's disease medicines

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

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

Tyramine/rasagiline interaction

It was reported that the results of four tyramine challenge studies (in volunteers and Parkinson's disease patients), together with results of home monitoring of blood pressure after meals (of 464 patients treated with 0,5 or 1 mg/day of rasagiline as in RAZAGIN 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 RAZAGIN can be used safely without dietary tyramine restrictions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

Breastfeeding

It is not known whether rasagiline is excreted in human milk.

Safety in lactation has not been demonstrated.

Fertility

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

4.7 Effects on ability to drive and use machines

In patients experiencing somnolence/sudden sleep episodes, rasagiline as in RAZAGIN may have a major influence on the ability to drive and use machines.

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

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

4.8 Undesirable effects

Summary of the safety profile

In clinical studies in Parkinson's disease patients the most commonly reported adverse reactions were headache, depression, vertigo, and flu (influenza and rhinitis) in monotherapy;

dyskinesia, orthostatic hypotension, fall, abdominal pain, nausea and vomiting, and dry mouth in adjunct to levodopa therapy; musculoskeletal pain, as back and neck pain, and arthralgia in both regimens. These adverse reactions were not associated with an elevated rate of medicine discontinuation.

Tabulated list of adverse reactions

Adverse reactions are listed below in Tables 1 and 2 by system organ class and frequency.

Table 1: Monotherapy

Infections and infestations

Frequent: influenza

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Less frequent: skin carcinoma – melanoma

Blood and lymphatic system disorders

Frequent: leukopenia

Immune system disorders

Frequent: allergic reaction

Metabolism and nutrition disorders

Less frequent: decreased appetite

Psychiatric disorders

Frequent: depression, hallucinations

Frequency not known: impulse control disorders *

Nervous system disorders

Frequent: headache

Less frequent: cerebrovascular accident

Frequency not known: serotonin syndrome*, excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes*

Eye disorders

Frequent: conjunctivitis

Ear and labyrinth disorders

Frequent: vertigo

Cardiac disorders

Frequent: angina pectoris

Less frequent: myocardial infarction

Vascular disorders

Frequency not known: hypertension*

Respiratory, thoracic and mediastinal disorders

Frequent: rhinitis

Gastrointestinal disorders

Frequent: flatulence, dyspepsia, anorexia

Skin and subcutaneous tissue disorders

Frequent: dermatitis, contact dermatitis, vesiculobullous rash

Musculoskeletal, connective tissue and bone disorders

Frequent: musculoskeletal pain, neck pain, back pain, arthritis, arthralgia

Renal and urinary disorders

Frequent: urinary urgency

General disorders and administration site conditions

Frequent: fever, malaise

* See section description of selected adverse reactions

Table 2: Adjunct therapy

Neoplasms benign, malignant and unspecified

Less frequent:	skin melanoma*

Metabolism and nutrition disorders

Frequent:	decreased appetite, weight loss

Psychiatric disorders

Frequent:	hallucinations*, abnormal dreams
Less frequent:	confusion
Frequency not known:	impulse control disorders*

Nervous system disorders

Frequent:	dyskinesia, dystonia, carpal tunnel syndrome, balance disorder, ataxia
Less frequent:	cerebrovascular accident
Frequency not known:	serotonin syndrome*, excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes*

Cardiac disorders

Less frequent:	angina pectoris

Vascular disorders

Frequent:	orthostatic hypotension*
Frequency not known:	hypertension *

Gastrointestinal disorders

Frequent: abdominal pain, constipation, nausea and vomiting, dry mouth, anorexia

Skin and subcutaneous tissue disorders

Frequent: rash

Musculoskeletal, connective tissue and bone disorders

Frequent: arthralgia, musculoskeletal pain as back and neck pain, tenosynovitis

Investigations

Frequent: decreased weight

Injury, poisoning and procedural complications

Frequent: fall

* see section description of selected adverse reactions

Description of selected adverse reactions

Orthostatic hypotension

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

Hypertension

Rasagiline selectively inhibits MAO-B and is not associated with increased tyramine sensitivity at the indicated dose (1 mg/day). In blinded placebo-controlled studies (monotherapy and adjunct) severe hypertension was not reported in any subjects in the rasagiline arm. In the post-marketing period, cases of elevated blood pressure, including rare serious cases of

hypertensive crisis associated with ingestion of unknown amounts of tyramine-rich foods, have been reported in patients taking rasagiline. In the post-marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking rasagiline.

Impulse control disorders

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

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

Excessive daily sleepiness (hypersomnia, lethargy, sedation, sleep attacks, somnolence, sudden onset of sleep) can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of excessive daily sleepiness has been reported post-marketing with rasagiline.

Cases of patients, treated with rasagiline and other dopaminergic medicines, falling asleep while engaged in activities of daily living have been reported. Although many of these patients reported somnolence while on rasagiline with other dopaminergic medicines, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported more than 1-year after initiation of treatment.

Hallucinations

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

Serotonin syndrome

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

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

Malignant melanoma

It was reported that the incidence of skin melanoma in placebo-controlled clinical studies was 2/380 (0,5 %) in rasagiline 1 mg as adjacent to levodopa therapy group vs. 1/388 (0,3 %) incidence in placebo group. Additional cases of malignant melanoma were reported during post-marketing period. These cases were considered serious in all reports.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website: https://www.sahpra.org.za/health-products-vigilance.

4.9 Overdose

Symptoms

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

Overdose can be associated with significant inhibition of both MAO-A and MAO-B. In a single-dose study healthy volunteers received 20 mg/day and in a ten-day study healthy volunteers received 10 mg/day. Adverse reactions were mild or moderate and not related to rasagiline treatment. In a dose escalation study in patients on chronic levodopa therapy treated with

10 mg/day of rasagiline, there were reports of cardiovascular adverse reactions (including hypertension and postural hypotension) which resolved following treatment discontinuation. These symptoms may resemble those observed with non-selective MAO inhibitors.

Management

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 5.4.1 Anti-Parkinsonism preparations

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 the beneficial effects of rasagiline, seen in models of dopaminergic motor dysfunction.

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

5.2 Pharmacokinetic properties

Absorption

Rasagiline is well absorbed, reaching peak plasma concentration (C_{max}) in approximately 0,5 hours. The absolute bioavailability of a single rasagiline dose is about 36 %.

Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60 % and 20 %, respectively, when the medicine 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

Patients with hepatic impairment:

It was reported that in subjects with mild hepatic impairment (Child Pugh score 5 to 6), AUC and C_{max} were increased by 80 % and 38 %, respectively. In subjects with moderate hepatic impairment (Child Pugh B), AUC and C_{max} were increased by 568 % and 83 %, respectively (see sections 4.3 and 4.4).

Patients with renal impairment

The pharmacokinetic characteristics of rasagiline in subjects with mild (CLcr 50-80 ml/min) and moderate (CLcr 30-49 ml/min) renal impairment were similar to healthy subjects.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose (E460)

Pregelatinised starch (maize)

Colloidal anhydrous silica

Malic acid (E296)

Stearic acid (E570)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep the blister strips in the carton until required for use.

6.5 Nature and contents of container

Aluminium-OPA/Alu/PVC blister packs of 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Holder of the Registration Certificate

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

South Africa

8. Registration number

50/5.4.1/0545

9. Date of first authorisation/renewal of the authorisation

18 January 2022

10. Date of revision of the text

Not applicable