PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RASAPAR 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg rasagiline (as 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 side. The diameter of the tablet is 8,5 mm ± 0,4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RASAPAR is indicated in adults for the treatment of idiopathic Parkinson's disease 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:

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

Special populations:

Elderly patients

No change in dose is required for elderly patients (see section 5.2).

Hepatic impairment

RASAPAR is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3). Caution should be used when initiating treatment with RASAPAR in patients with mild hepatic impairment. In case patients progress from mild to moderate hepatic impairment RASAPAR should be stopped (see section 4.4 and 5.2).

Renal impairment

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

Paediatric population:

Children and adolescents (< 18 years)

RASAPAR is not recommended as the safety and efficacy in children and adolescents have not been established.

Method of administration:

For oral use.

RASAPAR may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to rasagiline or to any of the excipients of RASAPAR (see section 6.1).
- Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicines and natural products available without prescription, e.g. St John's wort) or pethidine (see section 4.5).

At least 14 days must elapse between discontinuation of RASAPAR and initiation of treatment with MAO inhibitors or pethidine.

- Moderate to severe hepatic impairment or severe hepatic insufficiency (Child Pugh B and C).

4.4 Special warnings and precautions for use

Concomitant use of RASAPAR with other medicines:

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

The concomitant use of RASAPAR 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 RASAPAR and levodopa

Since RASAPAR potentiates the effects of levodopa, the adverse reactions of levodopa may be increased and preexisting dyskinesia exacerbated. Decreasing the dose of levodopa may ameliorate this adverse reaction.

There have been reports of hypotensive effects when RASAPAR was 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

RASAPAR may cause daytime drowsiness, somnolence, and, occasionally, 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 RASAPAR. 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 as in RASAPAR. Patients should be regularly monitored for the development of impulse control disorders. Patients and carergivers should be made aware of the behavioural symptoms of impulse control disorders that were observed in patients treated with RASAPAR, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

Melanoma:

During clinical development the occurrence of cases of melanoma prompted the consideration of a possible association with RASAPAR. The data collected suggest that Parkinson's disease, and not any medicine 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 RASAPAR in patients with mild hepatic impairment. RASAPAR use in patients with moderate to severe hepatic impairment is contraindicated. In case patients progress from mild to moderate hepatic impairment, RASAPAR should be discontinued (see section 5.2).

4.5 Interaction with other medicines and other forms of interaction

MAO inhibitors:

RASAPAR is contraindicated along with other MAO inhibitors (including medicines and natural products available 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 RASAPAR and pethidine is contraindicated (see section 4.3).

Sympathomimetics:

With MAO inhibitors there have been reports of medicine interactions with the concomitant use of sympathomimetic medicines. Therefore, in view of the MAO inhibitory activity of RASAPAR, concomitant administration of RASAPAR and sympathomimetics, such as those present in nasal and oral decongestants or cold medicines 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 nonselective MAO inhibitors. Therefore, in view of the MAO inhibitory activity of RASAPAR, the concomitant administration of RASAPAR and dextromethorphan is not recommended (see section 4.4).

Seletive serotonin-norepinephrine reuptake inhibitors (SNRIs) or selective serotonine reuptake inhibitors (SSRIs), tri- and tetracyclic antidepressants:

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

For concomitant use of RASAPAR with SNRIs/SSRIs 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 RASAPAR, 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 RASAPAR and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC of rasagiline by 83 %. Coadministration of RASAPAR and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either medicine. 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 RASAPAR in smoking patients could be decreased, due to induction of the metabolising enzyme CYP1A2.

Other cytochrome P450 isoenzymes:

In vitro studies showed that RASAPAR 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 RASAPAR multiple dosing), did not inhibit cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results
indicate that RASAPAR's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes (see section 5.3).

Levodopa and other Parkinson's disease medicines:

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

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

Tyramine/rasagiline interaction:

Results of four tyramine challenge studies (in volunteers and Parkinson's disease patients), together with results of home monitoring of blood pressure after meals (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 RASAPAR can be used safely without dietary tyramine restrictions.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no data from the use of RASAPAR in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of RASAPAR during pregnancy.

Breastfeeding:

Non-clinical data indicate that RASAPAR inhibits prolactin secretion and thus, may inhibit lactation.

It is not known whether RASAPAR is excreted in human milk. Caution should be exercised when RASAPAR is administered to a breastfeeding mother.

Fertility:

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

4.7 Effects on ability to drive and use machines

In patients experiencing somnolence/sudden sleep episodes, RASAPAR 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 RASAPAR does not affect them adversely.

Patients being treated with RASAPAR and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines), until they have gained sufficient experience with RASAPAR and other dopaminergic medicines to gauge whether or not it affects their mental and/or motor performance adversely.

If increased somnolence or new episodes of falling asleep during activities of daily living (e.g. watching television, passenger in a car, etc.) are experienced at any time during treatment, the patients should not drive or participate in potentially dangerous activities.

Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of RASAPAR.

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 RASAPAR, or when taking concomitant medicines that increase plasma levels of

RASAPAR (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 frequently 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 and elevated rate of medicine discontinuation.

List of adverse reactions:

Monotherapy

Infections and infestations

Frequent: Influenza.

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

Frequent: Skin carcinoma.

Blood and lymphatic system disorders

Frequent: Leucopenia.

Immune system disorders

Frequent: Allergy.

Metabolism and nutrition disorders

Less frequent: Decreased appetite.

Psychiatric disorders

Frequent: Depression, hallucinations*.

Frequency unknown: Impulse control disorders*.

Nervous system disorders

Frequent: Headache.

Less frequent: Cerebrovascular accident.

Frequency unknown: Seretonin syndrome*, excessive daytime sleepiness (EDS) and sudden sleep onset episodes*.

Eye disorders

Frequent: Conjunctivitis.

Ear and labyrinth disorders

Frequent: Vertigo.

Cardiac disorders

Frequent: Angina pectoris.

Less frequent: Myocardial infarction.

Vascular disorders

Frequency unknown: Hypertension*.

Respiratory, thoracic and mediastinal disorders

Frequent: Rhinitis.

Gastrointestinal disorders

Frequent: Flatulence, dyspepsia, anorexia.

Skin and subcutaneous tissue disorders

Frequent: Dermatitis.

Less frequent: Vesiculobullous rash.

Musculoskeletal and connective tissue disorders

Frequent: Musculoskeletal pain, neck pain, arthritis.

Renal and urinary disorders

Frequent: Urinary urgency.

General disorders and administration site conditions

Frequent: Fever, malaise.

* See section 'Description of selected adverse reactions' below.

Adjunct therapy

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

Less frequent: Skin carcinoma*.

Metabolism and nutrition disorders

Frequent: Decreased appetite.

Psychiatric disorders

Frequent: Hallucinations*, abnormal dreams.

Less frequent: Confusion.

Frequency unknown: Impulse control disorders*.

Nervous system disorders

Frequent: Dyskinesia, dystonia, carpal tunnel syndrome, balance disorder, ataxia.

Less frequent: Cerebrovascular accident.

Frequency unknown: Seretonin syndrome*, excessive daytime sleepiness (EDS) and sudden sleep onset episodes*.

Cardiac disorders

Less frequent: Angina pectoris.

Vascular disorders

Frequent: Orthostatic hypotension*.

Frequency unknown: Hypertension*.

Gastrointestinal disorders

Frequent: Abdominal pain, constipation, nausea and vomiting, dry mouth, anorexia.

Skin and subcutaneous tissue disorders

Frequent: Rash.

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia, neck pain, tenosynovitis.

Investigations

Frequent: Decreased weight.

Injury, poisoning and procedural complications

Frequent: Fall, accidental injury.

* See section ‘Description of selected adverse reactions’ below.

Description of selected adverse reactions:

Orthostatic hypotension

In blinded placebo-controlled studies, severe orthostatic hypotension was reported in one subject (0,3 %) 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 RASAPAR treatment and tends to decrease over time.

Hypertension

RASAPAR 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 RASAPAR. In the post-marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking RASAPAR.

Impulse control disorders (ICD)

One case of hypersexuality was reported in 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. Of the reported cases, at the time they were reported, only in a single case the patient had not recovered.

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 RASAPAR.

Cases of patients, treated with RASAPAR 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 RASAPAR 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 one 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 RASAPAR.

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-threatening 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 RASAPAR.

Malignant melanoma

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 RASAPAR is important. It allows continued monitoring of the benefit/risk balance of RASAPAR. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms:

Symptoms reported following overdose of RASAPAR 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 RASAPAR treatment. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of RASAPAR, 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 rasagaline 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 the 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. *Ex vivo* and *in vitro* experiments demonstrate that rasagiline is neither inhibitor nor inducer of major CYP450 enzymes (see section 4.5).

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 is linear with dose over the range of 0,5 to 2 mg in Parkinson's disease patients. Its terminal half-life is 0,6 to 2 hours.

Hepatic impairment:

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, 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 (CLcr 50 – 80 mL/min) and moderate (CLcr 30 – 49 ml/min) renal impairment were similar to healthy subjects.

Elderly:

Age has little influence on rasagiline pharmacokinetics in the elderly (> 65 years) (see section 4.2).

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Pregelatinised starch

Colloidal anhydrous silica

Malic acid

Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in carton until required for use.

6.5 Nature and contents of container

Silver aluminium-OPA/alu/PVC blister strips.

Pack sizes: 7, 10, 28, 30 or 100 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 CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

South Africa

8. REGISTRATION NUMBER

54/5.4.1/0701

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 September 2021

10. DATE OF REVISION OF THE TEXT