PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RASATRAX TABLETS (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RASATRAX TABLETS: Each tablet contains rasagiline mesylate equivalent to 1, 0 mg of rasagiline.

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

RASATRAX TABLETS: White to off-white, round, flat bevelled edged tablets debossed with “C13” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RASATRAX TABLETS 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

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

Special populations

Elderly:

No change in dosage is required.

Hepatic impairment:

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

Renal impairment:

No change in dosage is required.

Paediatric population (below 18 years):

RASATRAX TABLETS is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Method of administration

For oral use.

May be taken with or without food.

4.3 Contraindications

RASATRAX TABLETS is contraindicated:

- in patients with a history of hypersensitivity to the active substance rasagiline or to any of the excipients listed in 6.1.
- Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicines 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.

VR

- Moderate to severe hepatic impairment.

4.4 Special warnings and precautions for use

Concomitant use of rasagiline with other medicines

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

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

Concomitant use of rasagiline and levodopa

Since rasagiline 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 rasagiline 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

RASATRAX TABLETS 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 **RASATRAX TABLETS.** 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)

VR

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.

Melanoma

A retrospective cohort study suggested a possibly increased risk of melanoma with the use of rasagiline, especially in patients with longer duration of rasagiline exposure and/or with the higher cumulative dose of rasagiline. Any suspicious skin lesion should be evaluated by a specialist. Patients should therefore be advised to seek medical review if a new or changing skin lesion is identified.

Hepatic impairment

Caution should be used when initiating treatment with **RASATRAX TABLETS** in patients with mild hepatic impairment. **RASATRAX TABLETS** use in patients with moderate hepatic impairment should be avoided. In case patients progress from mild to moderate hepatic impairment, **RASATRAX TABLETS** should be stopped (see section 5.2).

4.5 Interaction with other medicines and other forms of interaction

MAO Inhibitors

RASATRAX TABLETS is contraindicated 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).

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 **RASATRAX TABLETS** and pethidine is contraindicated (see section 4.3).

VR

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 rasagiline, concomitant administration of rasagiline 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 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).

SNRI/SSRI/tri- and tetracyclic antidepressants

The concomitant use of **RASATRAX TABLETS** 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 uptake 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.

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 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.

CYP1A2 inducers

VR

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 at a concentration of 1 µg/ml (equivalent to a level that is 160 times the average C_{max} ~ 5.9-8.5 ng/ml in Parkinson's disease patients after 1 mg rasagiline multiple dosing), did not inhibit cytochrome P450 isoenzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

Levodopa and other Parkinson's disease medicinal products

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

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 (of 464 patients treated with 0.5 or 1 mg/day of rasagiline or placebo as adjunct therapy to levodopa for six months without tyramine restrictions), and the fact that there were no reports of tyramine/rasagiline interaction in clinical studies conducted without tyramine restriction, indicate that rasagiline can be used safely without dietary tyramine restrictions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

Breastfeeding

Safety during lactation has not been demonstrated.

VR

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

Rasagiline cause somnolence or sudden sleep episodes and it may have major influence on the ability to drive and use machines. Patients should be cautioned about operating hazardous machines, including motor vehicles or working at heights until they are reasonably certain that rasagiline does not affect them.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies in Parkinson's disease patients the 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 an elevated rate of medicine discontinuation.

Tabulated summary of adverse reactions

Monotherapy:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Influenza		
Neoplasms, benign, malignan10,t and unspecified (including cysts and polyps)	Skin carcinoma		

VR

Blood and lymphatic system disorders	Leucopenia		
Immune system disorders	Allergy Allergic reaction		
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders	Depression, Hallucinations		Impulse control disorders
Nervous system disorders	Headache	Cerebrovascular accident	Serotonin syndrome excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes
Eye disorders	Conjunctivitis		
Ear and labyrinth disorders	Vertigo		
Cardiac disorders	Angina pectoris	Myocardial infarction	
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders	Rhinitis		
Gastrointestinal disorders	Flatulence, anorexia, dyspepsia		
Skin and subcutaneous	Dermatitis, contact dermatitis,		

VR

tissue disorders	Skin carcinoma Vesiculobullous rash		
Musculoskeletal connective tissue and bone disorders	Musculoskeletal pain, neck pain, arthritis		
Renal and urinary disorders	Urinary urgency		
General disorders and administration site conditions	Fever Malaise		

Adjunct therapy

System organ class	Frequent	Less frequent	Frequency unknown
Neoplasms, benign, malignant and unspecified		Skin melanoma	
Metabolism and nutrition disorders	Decreased appetite Decreased weight		
Psychiatric disorders	Hallucinations Abnormal dreams	Confusion	Impulse control disorders
Nervous system disorders	Dyskinesia Dystonia Carpal tunnel syndrome balance disorder Abnormal dreams, ataxia	Cerebrovascular accident	Serotonin syndrome excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes

VR

Cardiac disorders	Angina pectoris		
Vascular disorders	Orthostatic hypotension		Hypertension
Gastrointestinal disorders	Abdominal pain, constipation, nausea and vomiting, dry mouth		
Skin and subcutaneous tissue disorders	Rash	Skin melanoma	

Musculoskeletal connective tissue and bone disorders	Arthralgia, neck pain, tenosynovitis		
Injury, poisoning and procedural complications	Fall		

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

VR

No cases of overdose have been reported in clinical studies

Overdose can be associated with significant inhibition of MAO.. 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 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.

5.2 Pharmacokinetic properties

Absorption

Rasagiline is rapidly 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 medicinal product is taken with a high fat meal. Because AUC is not substantially affected, rasagiline can be administered with or without food.

The mean volume of distribution following a single intravenous dose of rasagiline is 243 L. Plasma protein binding following a single oral dose of 14C-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. *Ex vivo* and *in vitro* experiments demonstrate that rasagiline is neither inhibitor nor inducer of major CYP450 enzymes (see section 4.5).

Following a single 20 mg 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

Elimination:

After oral administration of 14C-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 0.5-2 mg in Parkinson's disease patients. Its terminal half-life is 0.6-2 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).

VR

Renal impairment:

Rasagiline's pharmacokinetics characteristics in subjects with mild (CL cr 50-80 ML+/min) and moderate (CL cr 30-49 ML+/min) renal impairment were similar to healthy subjects.

Elderly:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Corn starch

Colloidal silicon dioxide

Anhydrous citric acid

Pregelatinized starch

Talc

Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for container.

36 months for blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

VR

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in a round white 60 HDPE container with a silica gel sachet and closed with a white child resistant closure packed in an outer carton. Pack sizes include 28's, 30'stablets.

Tablets are packed in aluminum foil laminated on one side and laminated to PVC on the other side. Pack sizes include 10's tablets or 28's tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

RASATRAX TABLETS : 56/5.4.1/0505

9. DATE OF FIRST AUTHORISATION

RASATRAX TABLETS : 24 October 2023

10. DATE OF REVISION OF THE TEXT

To be advised

VR