Approved Professional Information for Medicines for Human Use:

KINECT 1 mg

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KINECT 1 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1,44 mg rasagiline tartrate equivalent to 1 mg rasagiline.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

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

The diameter of the tablet is 8,5 mm ± 0,4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KINECT 1 mg 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 daily dose of KINECT 1 mg is 1 mg once daily with or without levodopa.

Special populations

Elderly population

No change in dosage is required for elderly patients.

Renal impairment

No change in dosage is required for renal impairment.

Hepatic impairment

KINECT 1 MG use in patients with moderate or severe hepatic impairment is contraindicated (see section 4.3). Caution should be used when initiating treatment with KINECT 1 MG in patients with mild hepatic insufficiency. In case patients progress from mild to moderate hepatic impairment KINECT 1 MG should be stopped (see section 4.4).

Paediatric population

Children and adolescents (<18 years): Not recommended as the safety and efficacy have not been established in this population.

Method of administration

KINECT 1 MG is for oral administration.

It may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to rasagiline tartrate or to any of the excipients of KINECT 1 mg listed in section 6.1.

- Concomitant treatment with other monoamine oxidase (MAO) inhibitors or pethidine (see section 4.5). At least 14 days should elapse between discontinuation of KINECT 1 MG and initiation of treatment with MAO inhibitors or pethidine.
- KINECT 1 mg is contraindicated in patients with moderate or severe hepatic insufficiency (Child Pugh B and C).

4.4 Special warnings and precautions for use

Dopamine Dysregulation Syndrome (DDS)

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder as a result of a compulsive pattern of dopaminergic medication misuse above doses adequate to control motor symptoms. The risk of DDS may occur in patients on chronic treatment with dopaminergic medicines used for Parkinson's disease. DDS consists of a series of complications such as compulsive use of dopaminergic medications, aggressive or hypomanic behaviours during excessive use, and withdrawal states characterised by dysphoria and anxiety, caused by long-term dopaminergic treatment in patients with Parkinson's disease.

Before initiation of treatment with KINECT 1 mg, patients and caregivers should be warned of the potential risk of developing DDS (see section 4.8).

Concomitant use of KINECT 1 mg with other medicine

The concomitant use of KINECT 1 mg 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 KINECT 1 mg. At least 14 days should elapse between discontinuation of KINECT 1 mg and initiation of treatment with fluoxetine or fluvoxamine.

The concomitant use of KINECT 1 mg 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 KINECT 1 mg and levodopa

Since rasagiline as in KINECT 1 mg 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 as in KINECT 1 mg 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 KINECT 1 mg may cause daytime drowsiness, somnolence, and, occasionally, especially if used with other dopaminergic medicine - 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 KINECT 1 mg. 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 KINECT 1 mg. 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 KINECT 1 mg, 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 KINECT 1 mg. The data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

Hepatic impairment

Caution should be used when initiating treatment with KINECT 1 mg in patients with mild hepatic impairment. KINECT 1 mg use in patients with moderate hepatic impairment should be avoided. In case patients progress from mild to moderate hepatic impairment, KINECT 1 mg should be stopped (See section 4.3).

4.5 Interaction with other medicines and other forms of interaction

MAO Inhibitors

KINECT 1 mg should not be administered along with other MAO inhibitors (including medicines and natural medicines without prescription e.g. St. John's Wort) as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crisis (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 KINECT 1 mg 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 rasagiline as in KINECT 1 mg, concomitant administration of KINECT 1 mg 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 rasagiline as in KINECT 1 mg, the concomitant administration of KINECT 1 mg and dextromethorphan is not recommended (see section 4.4).

SNRI/SSRI/tri- and tetracyclic antidepressants

The concomitant use of KINECT 1 mg 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), selective serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. Therefore, in view of the MAO inhibitory activity of rasagiline as in KINECT 1 mg, 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 KINECT 1 mg and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC of rasagiline by 83 %.

Co-administration of rasagiline as in KINECT 1 mg and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either medicines. Thus, potent CYP1A2 inhibitors may alter rasagiline as in KINECT 1 mg plasma levels and should be administered with caution.

CYP1A2 inducers

There is a risk that the plasma levels of rasagiline as in KINECT 1 mg 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 KINECT 1 mg 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 medicines

In Parkinson's disease patients receiving rasagiline as in KINECT 1 mg 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 KINECT 1 mg and entacapone increased rasagiline oral clearance by 28 %.

Tyramine/rasagiline interaction

It was reported that results of five 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 KINECT 1 mg 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 KINECT 1 mg can be used safely without dietary tyramine restrictions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. There are no data from the use of rasagiline as in KINECT 1 mg in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Avoid the use of KINECT 1 mg during pregnancy.

Breastfeeding

Non-clinical data indicate that rasagiline as in KINECT 1 mg inhibits prolactin secretion and thus, may inhibit lactation.

It is not known whether rasagiline is excreted in human milk. Safety in breastfeeding has not been established.

Fertility

No human data on the effect of rasagiline as KINECT 1 mg 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 KINECT 1 mg may have 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 KINECT 1 mg does not affect them adversely.

Patients being treated with KINECT 1 mg 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 KINECT 1 mg and other dopaminergic medications 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 KINECT 1 mg.

Patients should be cautioned about possible additive effects of sedating medicinal products, alcohol, or other central nervous system depressants (e.g. benzodiazepines, antipsychotics, antidepressants) in combination with KINECT 1 mg, or when taking concomitant medications that increase plasma levels of KINECT 1 mg (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 an elevated rate of medicine discontinuation.

Tabulated lists of adverse reactions

Frequency estimate:

Frequent (≥ 1/100)

Less frequent (< 1/100)

Not known (cannot be estimated from the available data).

Monotherapy

The tabulated list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies, in patients receiving rasagiline 1 mg / day.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	Influenza		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Skin carcinoma-melanoma		
Blood and lymphatic system disorders	Leucopenia		
Immune system disorders	Allergic reaction		
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders	Depression,		Impulse control

	Hallucinations*		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, dyspepsia, anorexia		
Skin and subcutaneous tissue disorders	Dermatitis, Vesiculobullous rash		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, back pain, Neck pain, Arthritis, arthralgia		
Renal and urinary disorders	Urinary urgency		
General disorders and administration site conditions	Fever, Malaise		
*See section description of selected adverse reactions			

Adjunct Therapy

The tabulated list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies in patients receiving rasagiline 1 mg /day.

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Skin melanoma*	
Metabolism and nutrition disorders	Decreased appetite, weight loss		
Psychiatric disorders	Hallucinations*, Abnormal dreams	Confusion	Impulse control disorders*
Nervous system disorders	Dyskinesia Dystonia, Carpal tunnel syndrome, Balance disorder, ataxia	Cerebrovascular accident	Serotonin syndrome*, Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes*
Cardiac disorders		Angina pectoris	

Vascular disorders	Orthostatic hypotension*		Hypertension*
Gastrointestinal disorders	Abdominal pain, constipation, Nausea and vomiting, dry mouth, anorexia		
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal and connective tissue disorders	Neck pain, arthralgia, tenosynovitis		
Investigations		Decreased weight	
Injury, poisoning and procedural complications	Accidental injury (primary falls)		
*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 subject 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 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 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 medicinal products, falling asleep while engaged in activities of daily living have been reported. Although many of these patients reported somnolence while on KINECT 1 mg with other dopaminergic medicinal products, 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 /daily, trazodone ≤ 100 mg /daily, citalopram ≤ 20 mg /daily, sertraline ≤ 100 mg /daily, and paroxetine ≤ 30 mg /daily (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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/health-products-vigilance

4.9 Overdose

Signs and symptoms

Symptoms reported following overdose of rasagiline as in KINECT 1 mg 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 as in KINECT 1 mg 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.

Treatment

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

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.

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 to 2 mg. Its terminal half-life is 0,6 to 2 hours.

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).

Renal impairment

Rasagiline's pharmacokinetic characteristics in subjects with mild (CLcr 50 to 80 mL / min) and moderate (CLcr 30 to 49 mL / min) renal impairment were similar to healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on the standard studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, reproduction and development.

Rasagiline did not present genotoxic potential *in vivo* and in several *in vitro* systems using bacteria or hepatocytes. In the presence of metabolite activation rasagiline induced an increase of chromosomal aberrations at concentrations with excessive cytotoxicity which are unattainable at the clinical conditions of use.

Rasagiline was not carcinogenic in rats at systemic exposure, 84 – 339 times the expected plasma exposures in humans at 1 mg /day. In mice, increased incidences of combined bronchiolar/alveolar adenoma and/or carcinoma were observed at systemic exposures, 144 – 213 times the expected plasma exposure in humans at 1 mg /day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)

Malic acid (E296)

Silica, colloidal anhydrous

Starch, pregelatinised (maize)

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 ºC.

6.5 Nature and contents of container

KINECT 1 mg 1 mg tablets are packed in Aluminium-OPA/Alu/PVC blisters. The blister packs are packed into cardboard cartons of 28’s or 30’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

51/5.4.1/0270

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT