Razylect®
Rasagiline Mesylate

FORMS AND PRESENTATION
Razylect® 0.5; Tablets; Box of 30.
Razylect® 1; Tablets; Box of 30.

COMPOSITION
Razylect® 0.5: Each tablet contains Rasagiline Mesylate equivalent to 0.5 mg Rasagiline.
Razylect® 1: Each tablet contains Rasagiline Mesylate equivalent to 1 mg Rasagiline.
Excipients: Microcrystalline cellulose, corn starch, colloidal silicon dioxide, anhydrous citric acid, pregelatinized starch, stearic acid.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
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.

Pharmacokinetic properties
Absorption
Rasagiline is rapidly absorbed, reaching peak plasma concentration (Cmax) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%.
Food does not affect the Tmax of rasagiline, although Cmax 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 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.

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.

INDICATIONS
Razylect® 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.

CONTRAINDICATIONS
• Hypersensitivity to the active substance or to any of the excipients.
• Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) or pethidine. At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine.
• Severe hepatic impairment.

PRECAUTIONS
Concomitant use of rasagiline with other medicinal products
The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided. At least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with rasagiline. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine.
Impulse control disorders (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.
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.
Concomitant use of rasagiline and dextromethorphan or sympathomimetics
The concomitant use of rasagiline and dextromethorphan or sympathomimetics such as those present in nasal and oral decongestants or cold medicinal product containing ephedrine or pseudoephedrine is not recommended.

Melanoma
During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. 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 rasagiline in patients with mild hepatic impairment. Rasagiline use in patients with moderate hepatic impairment should be avoided. In case patients progress from mild to moderate hepatic impairment, rasagiline should be stopped.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that Rasagiline does not affect them adversely.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
For rasagiline no clinical data on exposed pregnancies is available. Animals studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.
Breast-feeding
Experimental data indicated that rasagiline inhibits prolactin secretion and thus, may inhibit lactation.
It is not known whether rasagiline is excreted in human milk. Caution should be exercised when rasagiline is administered to a breast-feeding mother.

DRUG INTERACTIONS
There are a number of known interactions between non selective MAO inhibitors and other medicinal products.
- Rasagiline must not be administered along 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.
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 and pethidine is contraindicated.
With MAO inhibitors there have been reports of medicinal product interactions with the concomitant use of sympathomimetic medicinal products. 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 medicinal products, containing ephedrine or pseudoephedrine, is not recommended.
There have been reports of medicinal product 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.
- The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided.
- For concomitant use of rasagiline with selective serotonin reuptake inhibitors (SSRIs)/selective serotoninnorepinephrine reuptake inhibitors (SNRIs) in clinical trials.
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.

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- In Parkinson's disease patients receiving chronic levodopa treatment as adjunct therapy, there was no clinically significant effect of levodopa treatment on rasagiline clearance.
- In vitro metabolism studies have indicated that cytochrome P450 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of rasagiline. 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.
- There is a risk that the plasma levels of rasagiline in smoking patients could be decreased, due to induction of the metabolising enzyme CYP1A2.
- Concomitant administration of rasagiline and entacapone increased rasagiline oral clearance by 28%.
- Tyramine/rasagiline interaction: Rasagiline can be used safely without dietary tyramine restrictions.

ADVERSE EFFECTS

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 drug discontinuation.

Adverse reactions listed below by system organ class and frequency using the following conventions: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Monotherapy

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

Infections and infestations: Influenza (common).
Neoplasms benign, malignant and unspecified (including cysts and polyps): Skin carcinoma (common).
Blood and lymphatic system disorders: Leucopenia (common).
Immune system disorders: Allergy (common).
Metabolism and nutrition disorders: Decreased appetite (uncommon).
Psychiatric disorders: Depression, Hallucinations (common); Impulse control disorders (not known).
Nervous system disorders: Headache (very common); Cerebrovascular accident (uncommon); Serotonin syndrome, Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes (not known).
Eye disorders: Conjunctivitis (common).
Ear and labyrinth disorders: Vertigo (common).
Cardiac disorders: Angina pectoris (common); Myocardial infarction (uncommon).
Vascular disorders: Hypertension (not known).
Respiratory, thoracic and mediastinal disorders: Rhinitis (common).
Gastrointestinal disorders: Flatulence (common).
Skin and subcutaneous tissue disorders: Dermatitis (common); Vesiculobullous rash (uncommon).
Musculoskeletal and connective tissue disorders: Musculoskeletal pain, Neck pain, Arthritis (common).
Renal and urinary disorders: Urinary urgency (common).
General disorders and administration site conditions: Fever, Malaise (common).

Adjunct Therapy

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

Neoplasms benign, malignant and unspecified: Skin melanoma (uncommon).
Metabolism and nutrition disorders: Decreased appetite (common).
Psychiatric disorders: Hallucinations, Abnormal dreams (common); Confusion (uncommon); Impulse control disorders (not known).
Nervous system disorders: Dyskinesia (very common); Dystonia, Carpal tunnel syndrome, Balance disorder (common); Cerebrovascular accident (uncommon); Serotonin syndrome, Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes (not known).
Cardiac disorders: Angina pectoris (uncommon).
Vascular disorders: Orthostatic hypotension (common); Hypertension (not known).
Gastrointestinal disorders: Abdominal pain, Constipation, Nausea and vomiting, Dry mouth (common).
Skin and subcutaneous tissue disorders: Rash (common).
Musculoskeletal and connective tissue disorders: Arthralgia, Neck pain (common).
Investigations: Decreased weight (common).
Injury, poisoning and procedural complications: Fall (common).

DOSAGE AND ADMINISTRATION

Monotherapy

The recommended Razylect® dose for the treatment of Parkinson's disease patients is 1 mg administered once daily.

Adjunctive Therapy

The recommended initial dose is 0.5 mg administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Patients with Hepatic Impairment

Razylect® is contraindicated in patients with severe hepatic impairment . Razylect® use in patients with moderate hepatic impairment should be avoided. Caution should be used when initiating treatment with Razylect® in patients with mild hepatic impairment. In case patients progress from mild to moderate hepatic impairment rasagiline should be stopped.

Renal impairment

No special precautions are required in patients with renal impairment.

Paediatric population

Rasagiline is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Method of administration

For oral use.
Razylect® may be taken with or without food.

OVERDOSAGE

Symptoms

Symptoms reported following overdose of rasagiline 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.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of Revision: November 2020.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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