Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eldepryl 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of selegiline hydrochloride.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
A white or almost white, round, convex uncoated tablet having a single scoreline on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Eldepryl is indicated for the treatment of Parkinson's disease, or symptomatic parkinsonism. Eldepryl may be used alone in early Parkinson's disease to delay the need for levodopa (with or without decarboxylase inhibitor). Eldepryl may also be used in the management of patients with Parkinson's disease not adequately controlled by conventional therapy or in whom on-off symptoms or other dyskinesias develop during maximal levodopa therapy.

4.2 Posology and method of administration

Posology
Adults only:
5-10 mg daily either alone or as an adjunct to levodopa or levodopa/peripheral decarboxylase inhibitor. When Eldepryl is added to a levodopa regimen it is possible to reduce the levodopa dosage by an average of 30%.

Method of administration
Eldepryl may be administered either as a single dose in the morning or in two divided doses of 5 mg, taken at breakfast and lunch.

Special Populations

Hepatic impairment
No data are known on dose adjustment in patients with mild hepatic impairment.

Renal impairment
No data are known on dose adjustment in patients with mild renal impairment.

4.3 Contraindications

Hypersensitivity to selegiline or to any of the excipients of the product listed in section 6.1.

Selegiline should not be used in combination with selective serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitor (SNRI) (e.g. venlafaxine), tricyclic antidepressants, sympathomimetics, monoamine oxidase inhibitors (e.g. linezolide), and opioids (e.g. pethidine) (see section 4.5).

Selegiline should not be used in patients with active duodenal or gastric ulcer.

When selegiline is prescribed in combination with levodopa, the contraindications which apply to levodopa must be taken into account.

4.4 Special warnings and precautions for use

Since the selegiline potentiates the effect of levodopa, the side effects of levodopa may be more pronounced, especially if patients are receiving levodopa therapy with high doses. These patients should be monitored. The addition of selegiline to levodopa therapy may cause creation of involuntary movements and/or agitation. These undesirable effects disappear after levodopa doses reduction. Dosage of levodopa could be reduced to about 30 % in combination with selegiline.

Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as selegiline have been reported as exhibiting impulse control disorders and compulsions like pathological gambling, increased libido, hypersexuality, binge eating, shopping and different kinds of compulsive/repetitive activities (punding).

If selegiline is administered in higher doses than recommended (10 mg), selegiline may lose its MAO-B selectivity and therefore the risk of hypertension rises.

Special care should be taken administering selegiline to patients with peptic or duodenal ulceration, labile hypertension, cardiac arrhythmias, severe angina pectoris, severe liver or kidney dysfunction or psychosis as aggravation of these conditions may occur during treatment.

Selegiline should be used with caution in severe liver or kidney dysfunction.

Caution should be exercised in patients receiving MAO inhibitors during general anaesthesia in surgery. MAO inhibitors, including selegiline, may potentiate the effects of CNS depressants used for general anaesthesia. Transient respiratory and cardiovascular depression, hypotension and coma have been reported (see section 4.5).

Some studies concluded in an increased risk of mortality in patients receiving selegiline and levodopa compared to those receiving levodopa only. However, it is noteworthy that multiple methodological bias were identified in these studies and that a meta analysis and large cohort studies concluded that there was no significant difference in mortality in patients treated with selegiline to those treated with comparators or with the association selegiline/levodopa.

Studies have related the risk of an increased hypotensive response to concomitant administration of selegiline and levodopa, in patients with cardiovascular risk.

The addition of selegiline to levodopa may not be beneficial in those patients who experience fluctuations in response which are not dose dependent.

Caution is advised when selegiline is taken in combination with other centrally acting medicinal products and substances. The concomitant intake of alcohol should be avoided.

Buprenorphine
Concomitant administration of selegiline and buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with buprenorphine is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Association contra-indicated (*see section 4.3*)

At least two weeks should elapse after stopping administration of Eldepryl before starting therapy with any contra-indicated medicinal product.

Sympathomimetics
Because of the risk of hypertension, co-administration of selegiline and sympathomimetics is contraindicated.

Pethidine
The concomitant administration of the selective MAO-B inhibitor selegiline and pethidine is contraindicated.

Selective serotonin reuptake inhibitors (SSRIs)and serotonin noradrenaline reuptake inhibitors (SNRIs)

Because of the risk of confusion, hypomania, hallucination and manic episodes, agitation, myoclonus, hyperreflexia, incoordination, shivering, tremor, convulsion, ataxia, diaphoresis, diarrhea, fever, hypertension, which can be part of the serotonine syndrome, concomitant administration of selegiline and SSRIs or SNRIs is contraindicated.

Serious reactions with signs and symptoms that may include diaphoresis, flushing, ataxia, tremor, hyperthermia, hyper/hypotension, seizures, palpitation, dizziness and mental changes that include agitation, confusion and hallucinations progressing to delirium and coma have been reported in some patients receiving a combination of selegiline and fluoxetine. Similar experience has been reported in patients receiving selegiline and other serotonin reuptake inhibitors such as, sertraline, paroxetine, venlafaxine and fluvoxamine.

Although citalopram has generally less interactions than fluoxetine caution is advised on concomitant use of selegiline and citalopram. A minimum period of five weeks should be allowed between discontinuation of fluoxetine and initiation of selegiline treatment, due to the long half-lives of fluoxetine and its active metabolite. As the half-lives of selegiline and its metabolites are short, a wash-out period of 14 days after selegiline treatment would be sufficient before starting fluoxetine.

Tricyclic antidepressants
Severe CNS toxicity (serotonin syndrome) has been reported in patients with the combination of tricyclic antidepressants and selegiline. In one patient receiving amitriptyline and selegiline this included hyperpyrexia and death, and another patient receiving protriptyline and selegiline experienced tremor, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline was added.

Other adverse reactions occasionally reported in patients receiving a combination of selegiline with various tricyclic antidepressants include hyper/hypotension, dizziness, diaphoresis, tremor, seizures, and changes in behavioural and mental status. Therefore, the concomitant use of selegiline and tricyclic antidepressants is contraindicated.

MAO inhibitors
Concomitant administration of selegiline and MAO inhibitors may cause central nervous and cardiovascular system disorders (see section 4.4).

Associations not recommended

Tramadol and Buprenorphine
Tramadol and Buprenorphine are also potential interacting medications.

Oral contraceptives
Concomitant use of oral contraceptives (tablets containing the combination of gestodene/ethinyl estradiol or levonorgestrel/ethinyl estradiol) and selegiline may increase the bioavailability of selegiline. Thus, the concomitant administration of selegiline and oral contraceptives should be avoided.

Dopamine should be used with caution in patients receiving selegiline.

Concomitant treatment with medicinal products, with a narrow therapeutic index, such as digitalis and/or anticoagulants, requires caution and careful monitoring.

Food interactions
As selegiline is a specific MAO-B inhibitor, foods containing tyramine have not been reported to induce hypertensive reactions during selegiline treatment at recommended dosage (i.e. it does not cause the so-called "cheese-effect"). Therefore, no dietary restrictions are required. However, in case of combination of selegiline and conventional MAO inhibitors or MAO-A, dietary restrictions (i.e. avoidance of food with large amounts of tyramine such as aged cheese and yeast products) are recommended. When a combination of selegiline and moclobemide, an inhibitor of mono-amine oxidase-A, has been used together, the tyramine sensitivity factor may increase up to 8-9 (being 1 for selegiline alone and 2-3 for moclobemide alone).

4.6 Fertility, pregnancy and lactation

Pregnancy
Very limited data on pregnant patients are available. Studies in animals have shown reproductive toxicity only at high multiple of human doses. As a precautionary measure, it is preferable to avoid the use of selegiline in pregnancy.

Breast-feeding

It is unknown whether selegiline is excreted in human breast milk. The excretion of selegiline in milk has not been studied in animals. Physico-chemical data on selegiline point to excretion in breast milk and a risk to the suckling child cannot be excluded. Selegiline should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

As selegiline may cause dizziness, patients should be advised not to drive or use machines if they experience this adverse reaction during treatment.

4.8 Undesirable effects

In monotherapy, selegiline has been found to be well tolerated. Dry mouth, transient rise of serum alanine aminotransferase (ALAT) values and sleeping disorders have been reported more frequently than in patients receiving placebo.

In combination with levodopa
Since selegiline potentiates the effect of levodopa, side effects of levodopa (restlessness, hyperkinesis, abnormal movements, agitation, confusion, hallucination, postural hypotension, cardiac arrhythmias) may be enhanced in combined therapy (levodopa should be usually given in association with a peripheral decarboxylase inhibitor). Selegiline combination therapy may permit further reduction of levodopa dose (even by 30 %).

Micturition difficulties and skin reactions have also been reported during selegiline treatment. Follow-up of these possible adverse reactions is important.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. 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 established from the available data).

System Organ Class	Frequency	Undesirable Effects
Psychiatric disorders	**Common**	Sleeping disorders, confusion, hallucinations
	Uncommon	Mood change
	Not known	Impulse control disorders and compulsions (such as hypersexuality)*
Nervous system disorders	**Common**	Abnormal movements (such as dyskinesias), vertigo, dizziness, headache
	Uncommon	Mild transient sleep disorder
	Rare	Agitation
Cardiac disorders	**Common**	Bradycardia
	Uncommon	Supraventricular tachycardia
	Rare	Cardiac arrhythmias
Vascular disorders	**Rare**	Postural hypotension
Gastrointestinal disorders	**Common**	Nausea
	Uncommon	Dry mouth
Hepato-biliary disorders	**Common**	Transient rise of serum alanine aminotransferase (ALAT)
Skin and subcutaneous tissue	**Rare**	Skin reactions
Renal and urinary disorders	**Rare**	Micturition difficulties
	Not known	Urinary retention
Investigations	**Common**	Mild hepatic enzymes increased

* Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as selegiline have been reported as exhibiting impulse control disorders and compulsions like pathological gambling, increased libido, hypersexuality, binge eating, shopping and different kinds of compulsive/repetitive activities (punding).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance website: www.hpra.ie.

4.9 Overdose

No overdosage cases are known. Since the selective inhibition of MAO-B by selegiline is achieved only at doses recommended for the treatment of Parkinson's disease (5 to 10 mg/day) overdoses may resemble those observed with non-selective MAO-inhibitor (central nervous and cardiovascular system disorders). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600mg/day selegiline, suffered severe hypotension and psychomotor agitation.

Ovedoses have no specific clinical picture. Theoretically, over-dosage causes significant inhibition of both MAO-A and MAO-B and thus, symptoms of overdosage may resemble those observed with non-selective MAO-inhibitors (central nervous and cardiovascular system disorders). Symptoms of non selective MAO inhibitors overdosage can progress over 24 hours to include drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, tremor, severe headache, hallucination, alternating low and high blood pressure, vascular collapse, rapid and irregular pulse, precordial pain, respiratory depression and failure, severe muscle spasms, hyperpyrexia, diaphoresis, coma and convulsions). There is no specific antidote and treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoamine oxidase B inhibitors, ATC-code: N04BD01.

Selegiline is a selective MAO-B-inhibitor which prevents dopamine breakdown in the brain. It also inhibits the reuptake of dopamine at the presynaptic dopamine receptor. These effects potentiate dopaminergic function in the brain and help to even out and prolong the effect of exogenous and endogenous dopamine. Thus, selegiline potentiates and prolongs the effect of levodopa in the treatment of parkinsonism.

Double-blind studies on early phase Parkinsonian patients showed that patients receiving selegiline monotherapy manage significantly longer without levodopa therapy than controls receiving placebo. These patients could also maintain their ability to work longer.
The addition of selegiline to levodopa (with or without decarboxylase inhibitor) therapy helps to alleviate dose related fluctuations and end of dose deterioration.

When selegiline is added to such a regimen it is possible to reduce the levodopa dosage by an average of 30%. Unlike conventional MAO-inhibitors, which inhibit both the MAO-A and MAO-B enzyme, selegiline is a specific MAO-B inhibitor and can be given safely with levodopa.

Selegiline does not cause the so called cheese effect either when used alone as monotherapy, or when used with other drugs, except for moclobemide or nonselective MAO-inhibitors.

5.2 Pharmacokinetic properties

Absorption
Selegiline is readily absorbed from the gastro-intestinal tract. The maximal concentrations are reached in 0.5-0.75h after oral administration in fasting state. The bioavailability is low; 10% (on average, interindividual variation is large) of unchanged selegiline can reach the systemic circulation. Selegiline is a lipophilic, slightly basic compound, which quickly penetrates into tissues, also into brain.

Distribution
Selegiline is rapidly distributed throughout the body, the apparent volume of distribution being 500 l after an intravenous 10 mg dose. 75-85% of selegiline is bound to plama proteins at therapeutic concentrations. Selegiline inhibits enzyme MAO-B irreversibly and enzyme activity only increases again after new enzyme is synthesized. The strong inhibitory effect of platelet enzyme MAO-B activity after single 10 mg dose lasts over 24 h, and the platelet enzyme MAO-B activity returns to normal level approximately after 2 weeks.

Biotransformation
Selegiline is rapidly metabolised mainly in the liver, into active metabolites desmethylselegiline, l-methamphetamine and to l-amphetamine. In vitro studies indicate that CYP2B6 is the main hepatic cytochrome P450 (CYP) enzyme involved in the metabolism of selegiline with a possible contribution of CYP3A4 and CYP2A6. In humans, the three metabolites have been identified in plasma and urine after single and multiple doses of selegiline.

Elimination
The mean elimination half-life is 1.5-3.5 hours for selegiline. The total body clearance of selegiline is about 240 l/hour. The metabolites of selegiline are excreted mainly via the urine with approximately 15% occurring in the faeces.

5.3 Preclinical safety data

No mutagenicity or carcinogenicity due to selegiline has emerged in routine studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Maize starch
Microcrystalline cellulose
Povidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.Store in the original package in order to protect from light.

6.5 Nature and contents of container

White polyethylene bottle with polyethylene closure placed in cardboard outer carton and aluminium foil blister-packs placed in cardboard outer carton.

Pack sizes: 30, 50, 60, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA1327/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 January 1996

Date of last renewal: 03 January 2006

10 DATE OF REVISION OF THE TEXT

May 2023