SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Selegos 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of Selegiline hydrochloride.

Excipient with known effect: lactose monohydrate. Each 5 mg tablet contains 85 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round, white, flat, scored tablets with 7mm diameter.

4.0 CLINICAL PARTICULARS

4.1. Therapeutic indications

SELEGOS is indicated for the treatment of Parkinson's disease or symptomatic parkinsonism.
SELEGOS may be used alone in early Parkinson's disease to delay the need for levodopa (with or without decarboxylase inhibitor). SELEGOS may also be used as an adjunct to levodopa (with or without decarboxylase inhibitor).

4.2. Posology and method of administration

SELEGOS 10mg (2 tablets) daily either alone or as an adjunct to levodopa or levodopa/peripheral decarboxylase inhibitor.

SELEGOS may be administered either as a single dose in the morning or in two divided doses of 5mg taken at breakfast and lunch.
When SELEGOS is added to a levodopa regimen it is possible to reduce the levodopa dosage by an average of 30 per cent.

4.3. Contraindications

None.

4.4. Special warnings and precautions for use

The precise dose at which selegiline becomes a non-selective inhibitor of all MAO has not been determined, but with doses higher than 10 mg/day there is a theoretical risk of hypertension after ingestion of tyramine-rich food.
Concomitant treatment with medicines which inhibit MAO-A, (or non-selective MAO inhibitors) can cause hypotensive reactions.
Hypotension, sometimes sudden in onset, has been reported with conventional selegiline.
Serotonin syndrome
Concomitant administration of Selegos and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents 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.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.
Special care should be taken when administering selegiline to patients who have labile hypertension, cardiac arrhythmias, severe angina pectoris, psychosis or a history of peptic ulceration as aggravation of these conditions may occur during treatment.
Although serious hepatic toxicity has not been observed, caution is recommended in patients with a history of hepatic dysfunction.
Transient or continuing abnormalities with a tendency for elevated plasma concentrations of liver enzymes have been described during long-term therapy with conventional tablets of selegiline.

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.

Since selegiline potentiates the effects of levodopa, the adverse effects of levodopa may be increased. When selegiline is added to the maximum tolerated dose of levodopa, involuntary movements and agitation may occur. Levodopa should be reduced when selegiline is added to the treatment (see section 4.2 Posology and Method of Administration). When an optimum dose of levodopa is reached, adverse effects from the combination are less than those observed with levodopa on its own.

Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments 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). These may also be possible with selegiline but very few cases have been reported to date.

Selegos contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Tramadol and buprenorphine are also potential interacting medicaments.
Selegos should be used cautiously when co-administered with buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).
Selegiline should not be administered with any type of antidepressant.
Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs)
When selegiline is used at its recommended dose, it selectively inhibits MAO-B. The combined use of the SSRI, fluoxetine and Selegos, should only be used under clinical supervision.
Serious reactions with signs and symptoms that may include diaphoresis, flushing, ataxia, 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 two other serotonin reuptake inhibitors, sertraline and paroxetine. There is a potential risk of interaction with fluvoxamine and venlafaxine.

Use of Selegos beyond the recommended dose could lead to non-selectivity and serious adverse effects.
Death has been reported to occur following the initiation of therapy with non-selective MAO inhibitors shortly after discontinuation of fluoxetine. Fluoxetine should not be used less than 14 days after discontinuation of selegiline. Since fluoxetine has a very long elimination half-life, at least 5 weeks should be allowed after stopping fluoxetine and before starting selegiline.
Selegiline should not be started until 2 weeks after stopping sertraline. For all other serotonin reuptake inhibitors, a time interval of 1 week is recommended between discontinuation of the serotonin reuptake inhibitor and initiation of selegiline. In general, selegiline should not be introduced after a drug that is known to interact with selegiline, until after 5 half-lives of that drug have elapsed.
At least 14 days should lapse between the discontinuation of selegiline and initiation of treatment with any drug known to interact with selegiline.
A time interval of 24 hours is recommended between the discontinuation of selegiline and initiation of serotonin agonists.

Patients being treated with selegiline currently or within the past 2 weeks should receive dopamine only after careful risk-benefit assessment, as this combination enhances the risk of hypertensive reactions.

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.

MAO inhibitors

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

Associations not recommended

Oral contraceptives

The combination of selegiline and oral contraceptives or drugs for hormone replacement therapy, should be avoided, as this combination may increase the bioavailability of selegiline.

Concomitant administration of amantadine and anticholinergic drugs can lead to an increased occurrence of side-effects.

In view of the high degree of binding to plasma proteins by selegiline particular attention must be given to patients who are being treated with medicines with a narrow therapeutic margin / index, such as digitalis and/or anticoagulants.

Four patients receiving altretamine and a monamine oxidase inhibitor experienced symptomatic hypotension after four to seven days of concomitant therapy.

Concomitant use of hypertensive agents, antihypertensives, psychostimulants, central suppressant drugs (sedatives, hypnotics) and alcohol should be avoided.

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.

4.6. Fertility, pregnancy and lactation

Selegiline is indicated for the treatment of Parkinson's disease which, in most cases, is a disease occurring after childbearing age.

The available safety data concerning the use during pregnancy and lactation is insufficient to justify the use of selegiline in these patient groups.

Pregnancy

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.

4.7. Effects on ability to drive and use machines

Even when used correctly, this medicine may cause dizziness or can affect reaction capacity to the extent that driving or operating machinery is affected and therefore patients should be advised not to drive or use machines if they experience these adverse reactions during treatment.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8. Undesirable effects

The following undesirable effects have been reported with selegiline during clinical trials and/or post-marketing use. They are listed below as MedDRA preferred term by system organ class and frequency. 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**
Infections and infestations	Uncommon	Pharyngitis
Blood and lymphatic system disorders	Uncommon	Leucocytopenia, thrombocytopenia
Metabolism and nutrition	Uncommon	Loss of appetite

disorders		
Psychiatric disorders	Common	Sleeping disorders, confusion, hallucinations, depression
	Uncommon	Abnormal dreams, agitation, anxiety, psychoses, mood change
	Not known	Hypersexuality*
Nervous system disorders	Common	Abnormal movements (such as dyskinesias, akinesia, bradykinesia), dizziness, headache, impaired balance, tremor
	Uncommon	mild transient sleep disorder
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Bradycardia
	Uncommon	Arrhythmias, palpitations, angina pectoris, supraventricular tachycardia
Vascular disorders	Common	hypotension, hypertension
	Uncommon	Orthostatic hypotension
	Rare	Postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion, sore throat
	Uncommon	Dyspnoea
Gastrointestinal disorders	Very common	Stomatitis
	Common	Nausea, constipation, diarrhoea, mouth ulceration
	Uncommon	Dry mouth
Hepato-biliary disordrers	Uncommon	Transient rise of serum alanine aminotransferase (ALAT)
Skin and subcutaneous tissue	Common	Sweating increased
	Uncommon	Hair loss, skin eruptions
	Rare	Skin reactions
Muskuloskeletal and lymphatic system disorders	Common	Arthralgia, back pain, muscle cramps
	Uncommon	Myopathy
Renal and urinary disorders	Uncommon	Micturition disorders
	Not known	Urinary retention
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Chest pain, irritability, ankle oedema
Injury, poisoning and procedural complications	Common	Fall
Investigations	Common	Mild hepatic enzymes increased

* Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments 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). These may also be possible with selegiline but very few cases have been reported to date.

As selegiline potentiates the effect of levodopa (levodopa should be usually given in association with a peripheral decarboxylase inhibitor), the side-effects of levodopa may be emphasised unless the dosage of levodopa is reduced. Selegiline combination therapy may permit further reduction of levodopa dose (even by 30 %). The most common undesirable effect reported for conventional tablets is dyskinesia (4% of patients) other side effects include restlessness, hyperkinesis, abnormal movements, agitation, confusion, hallucination, postural hypotension, cardiac arrhythmias. Once the optimum levodopa dose level has been established, the side-effects produced by the combination will usually be less than those caused by the levodopa therapy on its own.

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 national reporting system.

4.9. Overdose

Selegiline is rapidly metabolised and the metabolites rapidly excreted. In cases of suspected overdosage the patient should be kept under observation for 24 to 48 hours.

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). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg/day selegiline suffered severe hypotension and psychomotor agitation.

Theoretically, overdosage causes significant inhibition of both MAO-A and MAO-B and thus, symptoms of overdosage may resemble those observed with non-selective MAO-inhibitors which can progress over 24 hours to include, different central nervous and cardiovascular system disorders. These include agitation, irritability, hyperactivity, drowsiness, tremor, severe headache, hallucination, alternating low and high blood pressure dizziness, faintness, 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 the treatment is symptomatic.

5.0 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. Since it does not interfere with the breakdown of 5 hydroxytryptamine (serotonin) or noradrenaline, it does not cause any hypertensive crises or changes in the plasma or urinary metabolites of these monoamines.
Although dietary restrictions are not necessary during selegiline treatment, the inhibition of MAO B in blood platelets can lead to a slight potentiation of the circulatory effects of any tyramine not broken down by gastrointestinal MAO A during absorption.
The magnitude of increase in the urinary excretion of β phenylethylamine over 24 hours is simply related to the area under the selegiline plasma concentration-time curve after any selegiline product. Urinary β phenylethylamine increase reflects the degree of inhibition of MAO B.
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 HCl 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 HCl is readily absorbed from the gastrointestinal tract. The maximal concentrations are reached in 0.5-0.75h after oral administration in fasting state. The bioavailability is low; 10% (on the 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 1 after an intravenous 10 mg dose. 75-85% of selegiline is bound to plasma proteins at therapeutic concentrations. Selegiline HCl inhibits enzyme MAO-B irreversibly and enzyme activity only increases again after new enzyme is synthesised. The strong inhibitory effect 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, with elimination half-lives of 2.1h, 20.5 h and 17.7 h respectively. 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.

Selegiline AUC and desmethylselegiline AUC increase 2.7 fold and 1.5 fold respectively from day 1 to day 8 on dosing 10 mg od.

However, the half-lives of selegiline (range, 1.5-3.5 h) and desmethylselegiline (range, 3.4 – 5.3 h) were found to be relatively short. Accordingly, the short half-lives of these compounds failed to predict the apparent accumulation.

The most likely explanation for the significant increase in selegiline and desmethylselegiline concentrations in serum which was observed during the 8-day

multiple dose administration of selegiline HCl is saturation of MAO-B binding sites in tissues, as the rapid elimination of both selegiline and desmethyl selegiline cannot explain the apparent accumulation observed. However, decrease in the first-pass metabolism of selegiline on multiple dosing cannot be ruled out.

Elimination

In humans, the three metabolites have been identified in plasma and urine after single and multiple doses of selegiline. The mean elimination half-life is 1.5-3.5 h for selegiline. The total body clearance of selegiline is about 240 I/h. The metabolites of selegiline are excreted mainly via the urine with about 15% occurring in the faeces.

5.3. Preclinical safety data

Selegiline has not been sufficiently tested for reproductive toxicity. Studies with selegiline revealed no evidence of mutagenic or carcinogenic effects. The only safety concerns for human use derived from animal studies were effects associated with an exaggerated pharmacological action.

6.0. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Selegos 5 mg tablets also contain lactose monohydrate, povidone K25, maize starch, talc and magnesium stearate.

6.2. Incompatibilities

No other incompatibilities noted.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store below 30^0C, in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container

Selegos tablets are packed in the following: PVC/PCTFE film-aluminium foil blisters of ten tablets, in packs of 10, 50, 100, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. MANUFACTURER

Medochemie Ltd (Central Factory), 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. DATE OF REVISION OF THE TEXT

12/08/2021