Selgene

Selegiline hydrochloride

alphapharm

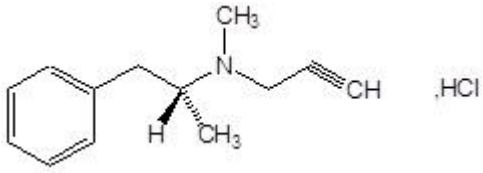
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Selegiline hydrochloride

Chemical name : (R)-methyl(α-methylphenethyl)-prop-2-ynylamine hydrochloride

Structural formula :



Molecular formula : $C_{13}H_{17}N$,HCl

Molecular weight : 223.75

CAS Registry no. : 14611-52-0

DESCRIPTION

Selegiline hydrochloride is a white to near white crystalline powder, freely soluble in water, chloroform and methanol. Each Selgene tablet contains 5 mg of selegiline hydrochloride. The tablets also contain lactose, maize starch, citric acid monohydrate, povidone, purified talc and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Selegiline is an irreversible inhibitor of MAO, an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline acts as a "suicide" substrate for MAO, i.e. it is converted by MAO to an active moiety which combines irreversibly with the active site of the enzyme and/or the enzyme's essential flavine adenine dinucleotide (FAD) cofactor. MAOs are currently subclassified into two types, A and B. MAO type A (MAO-A) and MAO type B (MAO-B) differ in their substrate specificity and tissue distribution. In humans most of the MAO in the brain is type B, while intestinal MAO is predominantly type A. At the recommended dose, selegiline's affinity for type B active sites is greater than for type A, and it serves as a selective inhibitor of MAO-B. However, this selectivity is dose dependent and at higher than recommended doses (>20 mg/day), it may be lost, resulting in increased inhibition of MAO-A. The precise dose at which selegiline becomes a nonselective inhibitor of all MAO is unknown.

The rate of MAO-B regeneration following discontinuation of selegiline treatment is dependent upon *de novo* protein synthesis. This rate, which has not been quantified, seems likely to determine how fast normal MAO-B activity can be restored. MAO plays an important role in the catabolism of catecholamines (dopamine, noradrenaline and adrenaline) and serotonin in CNS neurones. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. For example, it is believed that MAO in the gut and liver (primarily type A) provides essential protection from exogenous amines, e.g. tyramine. If absorbed intact, these amines can cause a hypertensive crisis, the so called "cheese reaction". This has been documented with nonselective monoamine oxidase inhibitors (MAOIs).

To date, there have been no reports of "cheese reactions" in patients treated with selegiline. However, the pathophysiology of the "cheese reaction" is complicated and is not fully understood. Selegiline's apparent freedom from this reaction has also been ascribed to its selective inhibition of MAO-B at clinically used doses

(≤10 mg/day) and its ability to prevent noradrenaline from being displaced from adrenergic neurones by tyramine and other indirect acting sympathomimetics (see **PRECAUTIONS**).

Selegiline may have pharmacological effects unrelated to MAO-B inhibition. There is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine reuptake at the synapse. Selegiline's effects may also be mediated through its metabolites, with three of its principal metabolites possibly having their own pharmacological actions. Two metabolites, l-amphetamine and l-methamphetamine interfere with neuronal uptake and enhance release of several neurotransmitters (e.g. noradrenaline, dopamine, serotonin). However, l-amphetamine and l-methamphetamine have significantly less activity than their corresponding d-isomers. The third metabolite, N-desmethylselegiline, appears to act as a selective inhibitor of MAO-B in animal studies. The extent to which each of these metabolites contributes to the effects of selegiline is unknown.

Pharmacokinetics

General characteristics.

Selegiline is readily absorbed from the gastrointestinal tract. The maximum concentrations are reached in 0.5 hours after oral administration. The bioavailability is low, on average 9.4 ± 5.9% of unchanged selegiline from a 10 mg oral dose reaches the systemic circulation. A substantial increase in selegiline bioavailability (up to threefold) occurs when selegiline is administered with food high in fat.

Selegiline is a lipophilic, slightly basic compound which quickly penetrates into tissues, including the brain. It is rapidly distributed throughout the body, with the apparent volume of distribution being 508 ± 182 L after a 10 mg intravenous dose. Selegiline is strongly bound to plasma proteins, especially to macroglobulins and, to a lesser extent, to albumin.

Selegiline is rapidly metabolised, mainly in the liver, into N-desmethylselegiline (the major metabolite), l-methamphetamine and l-amphetamine. In humans, these three metabolites have been identified in plasma and urine after single and multiple doses of selegiline. Following the oral administration of a single dose of selegiline hydrochloride 10 mg, for example, N-desmethylselegiline (mean $t_{½}$ 2 hours); l-amphetamine (mean $t_{½}$ 17.7 hours); and l-methamphetamine (mean $t_{½}$ 20.5 hours) were found in the serum and urine. Metabolites of selegiline are excreted mainly via the urine, with about 15% occurring in the faeces. Over a period of 48 hours, urinary excretion of these metabolites accounted for 45% of the dose administered. The mean elimination half-life of a 10 mg intravenous dose of selegiline is 1.6 +/- 0.3 hours. The total body clearance of selegiline is about 240 L/hour. The half-life of a 10 mg oral dose of selegiline is 1.2 to 1.8 hours.

Characteristics in patients.

Selegiline is metabolised quickly, but due to irreversible MAO-B inhibition, the duration of clinical effect does not depend on the elimination time of selegiline, and therefore once-daily dosing can be applied.

No information is available yet concerning polymorphic metabolism or the effect of renal or hepatic insufficiency on the metabolism of selegiline. Preliminary information on the pharmacokinetics of selegiline and its metabolites is available.

CLINICAL TRIALS

Selegiline as monotherapy in the early phase of Parkinson's disease

Four randomised, double blind, placebo controlled, parallel group studies, involving 501 patients treated with selegiline and 498 patients treated with placebo, have been conducted to the end of 1994 where the primary outcome measure was time to initiation of levodopa. The largest trial, the DATATOP study, randomised 800 patients to four different treatment regimens. These regimens were selegiline (10 mg once daily); vitamin E; a combination of selegiline with vitamin E; and placebo. The primary outcome measure was time to requirement for levodopa as additional therapy. An analysis of the primary endpoint at 12 months into the trial showed that, of those patients who were treated with selegiline, 97/399 (24.3%) had progressed to the point of requiring additional therapy (levodopa). Of those patients who had received vitamin E or placebo, 176/401 (43.9%)

required the addition of levodopa. The results demonstrated that selegiline delayed onset of the stage where levodopa was required, the delay in commencement of levodopa being approximately seven to nine months in the particular group studied. Overall, selegiline was shown in these four studies to significantly delay the need to introduce levodopa by five to nine months, compared to the placebo group. Evidence was less clear as to whether selegiline exerted a symptomatic effect.

Selegiline as adjunctive therapy in the early and middle phases of Parkinson's disease

Six randomised, double blind, placebo controlled, parallel or crossover studies, involving 157 patients treated with selegiline in combination with levodopa and 157 patients treated with placebo in combination with levodopa, have been conducted in patients in the early and middle phases of Parkinson's disease to the end of 1995. When levodopa was added to selegiline therapy, or both drugs were given together, to de novo patients with Parkinson's disease, optimal clinical conditions, in terms of disability, were maintained with levodopa doses 50 to 80% lower than if selegiline was not co-administered. Increases in daily levodopa dosage were significantly smaller in the selegiline and levodopa group, compared to the placebo and levodopa group, over time (up to five years). Levodopa dosing frequency was significantly in favour of patients on selegiline and levodopa compared to those on placebo and levodopa (i.e. less levodopa doses/day in the former group). Additionally, patients treated with selegiline and levodopa had attenuated deterioration in their disability scores, compared to the placebo and levodopa group. The conclusions from these studies were that the need to increase levodopa dose was slowed down.

INDICATIONS

Treatment of patients with Parkinson's disease. It can be used as monotherapy in the early phases of the disease and as adjunctive therapy with levodopa (with/without a peripheral decarboxylase inhibitor).

CONTRAINDICATIONS

Known hypersensitivity to selegiline or any of the other ingredients of this product.

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

Selective serotonin reuptake inhibitors (SSRIs).

The combination of SSRIs with selegiline is contraindicated because of reports of serious, sometimes fatal, reactions in patients receiving these combinations and in patients who have recently discontinued SSRIs and are then started on an MAOI. Agitation, ataxia, cold sweats, hypertension, mania, pseudophaeochromocytoma, 'serotonergic reaction' and shivers have been reported with the concomitant use of selegiline and SSRI's, particularly fluoxetine. Similar experience has been reported in patients receiving selegiline and venlafaxine.

The mechanism of the interaction between SSRIs and MAOIs is not fully understood, it is recommended to avoid the combination of selegiline and SSRIs. Although citalopram has generally less interactions than fluoxetine, caution is advised on concomitant use of selegiline and citalopram.

At least five weeks should be allowed between discontinuation of, for example, fluoxetine, sertraline or paroxetine and initiating selegiline therapy, due to the long half life of these SSRI drugs and/or their active metabolites. A period of two weeks between stopping selegiline and starting SSRI's is sufficient, because of the short half life of selegiline and its active metabolites.

Pethidine.

The combination of pethidine and MAOIs is contraindicated because of reports of serious, sometimes fatal, reactions in patients receiving this combination. These reactions have also been reported in patients who have been started on pethidine within two weeks of discontinuing an MAOI. (This warning is often extended to other opioids). Agitation, delirium, hyperpyrexia, irritability, restlessness, rigidity, stupor and sweating have been reported with the concomitant use of selegiline and pethidine. The mechanism of the interaction is not fully understood.

PRECAUTIONS

General

Daily doses of selegiline HCl exceeding those recommended (10 mg/day) should not be used because of the risks associated with non-selective inhibition of MAO, i.e. 'cheese reactions' (see **PHARMACOLOGY**). In higher doses (> 20 mg/day), the selectivity of selegiline starts to diminish, resulting in increased inhibition of MAO-A. The possibility of a hypertensive reaction at higher doses (> 20 mg/day) of selegiline after ingestion of food or drugs rich in various exogenous amines has to be taken into account. Even at the recommended dose of 10 mg/day the selectivity of selegiline for MAO-B may not be absolute. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown.

Some patients on adjunctive therapy may experience exacerbation of levodopa-associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive postsynaptic receptors. These effects may often be mitigated by reducing the dose of levodopa by approximately 10-30 %.

Selegiline should be used cautiously in patients with severe liver or kidney dysfunction, as there is no pharmacokinetic information available on selegiline or its metabolites in these patients (see **PHARMACOLOGY – Pharmacokinetics**).

Selegiline should be given cautiously to patients with severe angina pectoris, cardiac arrhythmias, labile hypertension, peptic or duodenal ulcer or psychosis, as selegiline may exacerbate these conditions.

Transient increases in hepatic transaminases have been reported during selegiline treatment (see A**DVERSE EFFECTS**).

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).

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 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.

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.

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 **INTERACTIONS WITH OTHER MEDICINES**).

Carcinogenicity

Selegiline showed no evidence of carcinogenicity in a 78 week study in mice at dietary levels up to 30 mg/kg/day and a 104 week study in rats at dietary levels up to 17.5 mg/kg/day.

Genotoxicity

Selegiline did not induce gene mutations in *Salmonella typhimurium* or chromosomal damage in an *in vivo* chromosomal aberration assay. No definitive mammalian gene mutation assay has been performed.

Effects on Fertility

Selegiline did not impair fertility in rats at oral doses up to 100 mg/kg/day.

Use in Pregnancy (Category B2)

Insufficient animal reproduction studies have been performed to conclude that selegiline poses no teratogenic risk. However, no evidence of a teratogenic effect was observed in one rat study carried out at doses of up to 180 times the recommended human dose.

The effects of selegiline in human pregnancy are unknown. The available safety data concerning the use of selegiline during pregnancy is insufficient to justify use in this patient group. Selegiline should not be given to pregnant women unless the expected benefit clearly outweighs any potential risk.

Use in Lactation

It is not known whether selegiline is excreted in human milk. The excretion of selegiline in milk has not been studied in animals. Physio-chemical data in selegiline point to excretion in breast milk and a risk to the suckling child cannot be excluded. Selegiline should not be given to breastfeeding mothers.

Paediatric Use

The effects of selegiline in children have not been evaluated.

INTERACTIONS WITH OTHER MEDICINES

Selective serotonin reuptake inhibitors (SSRIs)

The use of SSRIs in combination with selegiline is contraindicated (see **CONTRAINDICATIONS**).

Pethidine

The use of pethidine in combination with selegiline is contraindicated (see **CONTRAINDICATIONS**).

Monoamine oxidase inhibitors (MAOIs)

Moclobemide:

No tolerability problems have been reported when selegiline and moclobemide, a reversible inhibitor of MAO-A, have been used in combination. However, when used together, the exogenous amine sensitivity factor may increase. A diet low in exogenous amines such as tyramine is recommended for patients taking the combination.

Concomitant administration of selegiline and MAO inhibitors may cause central nervous and cardiovascular system disorders.

Non-selective MAOIs:

Combined use of non-selective MAOIs (including linezolid) with selegiline may cause severe hypertension or hypotension.

Serotonergic drugs

Treatment with heterogenous serotonergic drugs in patients primarily with psychiatric illness taken alone or in combination with other drugs such as MAOIs, has been uncommonly associated with symptoms of myoclonus, tremor, confusion, restlessness, ataxia and hyperreflexia (see **CLINICAL TRIALS**). While usually short-lived, this syndrome can lead to intensive care admissions and is potentially fatal. The occurrence of the serotonin syndrome may occur after use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants, 3-4-methylenedioxy-metamphetamine (MDMA or ecstasy) and other 5-HT

potentiating agents, and the antipsychotic drug, clozapine. The treatment of choice is cessation of the drugs responsible. Treatment with 5-HT receptor antagonists cyproheptadine, methysergide and propranolol may shorten the syndrome duration.

Tricyclic antidepressants (TCAs)

Severe CNS toxicity has been reported in patients when a combination of tricyclic antidepressants and selegiline has been used. In one patient receiving amitriptyline and selegiline this included hyperpyrexia and death; 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 hypertension/hypotension, dizziness, diaphoresis, tremor, seizures and changes in behavioural and mental status. Since the mechanisms of these reactions are not fully understood, concomitant use of selegiline with tricyclic antidepressants is not recommended.

At least two weeks should be allowed between discontinuation of a tricyclic antidepressant and initiation of selegiline therapy, due to the long $t_{½}$ of some tricyclics and their active metabolite(s). A two week period between selegiline discontinuation and tricyclic antidepressant initiation would be sufficient, because of the short $t_{½}$ of selegiline and its active metabolites.

Oral Contraceptives

Concomitant use of oral contraceptives (tablets containing the combination of gestodene/ethinyl estradiol or levonorgestrel/ethinyl estradiol) and selegiline may cause an increase in the oral bioavailability of selegiline. Thus, caution should be used during the concomitant administration of selegiline and oral contraceptives.

Other

In clinical trials, interactions between dopamine and selegiline have been reported occasionally resulting in a hypertensive reaction.

There have also been reports that concomitant use of tramadol with selegiline may adversely interact.

During selegiline treatment, the possibility of a hypertensive reaction as a result of an interaction with indirect sympathomimetic drugs has to be taken into account. Foods containing various exogenous amines such as tyramine have not been reported to induce hypertensive reactions during selegiline treatment at doses used in the treatment of Parkinson's disease.

ADVERSE EFFECTS

In monotherapy, selegiline has been found to be well tolerated. Dry mouth, transient rise of serum alanine aminotransferase values and sleeping disorders have been reported more frequently than in patients receiving placebo. Because selegiline potentiates the clinical efficacy of levodopa, the adverse reactions of levodopa, e.g. abnormal movements such as dyskinesias, nausea, agitation, confusion, hallucinations, headache, postural hypotension, cardiac arrhythmias and vertigo, may worsen when selegiline is added to the maximum tolerated levodopa dose. Micturition difficulties and skin reactions have also been reported during selegiline treatment. Follow-up of these possible adverse reactions is important.

Clinical trials

Table 1 summarises the adverse events reported in patients enrolled in double blind placebo-controlled trials where selegiline had been used as monotherapy or as adjunctive therapy with levodopa. Included are all adverse events which occurred with an incidence of 1% or greater in any treatment group. An asterisk represents an incidence of < 1% for that treatment group; a dash indicates that the adverse event was not reported.

Table 1: Percentage of adverse events (with an incidence ≥1%) reported in double blind, placebo-controlled trials using selegiline monotherapy or adjunctive therapy (with levodopa) in Parkinson's disease to the end of 1995.

Body System	Adverse Reaction	Monotherapy		Adjunctive Therapy			
				Earlier Phases		Late Phase	
		Selegiline n = 526	Placebo n = 523	Selegiline n = 157	Placebo n = 157	Selegiline n = 363	Placebo n = 358
Autonomic Nervous System	Dry mouth	*	*	21	21.7	7.2	2.8
	Sweating	*	*	5.1	5.7	4.1	3.1
Body (as a whole)	Fatigue	*	*	26.1	19.7	4.4	3.4
	Headache	2.1	2.1	9.6	4.5	1.7	*
	Oedema	*	*	7.6	3.8	-	-
	Syncope	-	-	6.4	3.8	2.8	2.2
Cardiovascular	Angina pectoris	-	-	7.6	2.5	-	-
	Arrhythmia	1.7	*	5.7	5.1	-	-
	Hypotension – postural	-	-	21	9.6	4.4	2.2
	Palpitation	-	-	10.8	8.9	-	-
Central Nervous System	Dizziness	1.5	1.5	3.2	2.5	3.6	
	Dyskinesia	-	-	1.3	*	8.8	2.5
	Hyperkinesia	-	-	-	-	1.4	*
	Involuntary movement (mouth)	*	*	2.5	3.8	-	-
	Vertigo	1.1	*	25.5	22.3	-	-
Gastrointestinal	Abdominal pain	*	*	-	-	1.1	*
	Anorexia	*	*	10.2	7.6	-	-
	Constipation	-		25.5	17.8	3	2
	Diarrhoea	-	-	3.8	9.6	-	-
	Eructation	-	-	7.6	5.1	-	-
	Gastric irritation	-	-	1.3	*	-	-
	Hiccup	-	-	3.8	3.2	-	-
	Nausea	3.8	3.6	24.2	12.1	7.7	2.2
	Vomiting	-	-	3.2	1.9	*	*
Liver and Biliary	ALT increased	5.9	2.7	-	-	-	-
	AST increased	5.3	2.5	-	-	-	-
Musculoskeletal	Musculoskeletal injuries	5.5	2.3	-	-	-	-

Psychiatric	Anxiety	*	*	12.1	12.1	1.1	*
	Confusion	-	-	6.4	1.9	1.7	*
	Depression	*	*	8.3	8.9	3	2.8
	Dreaming – abnormal	-	-	1.9	1.3	1.1	2
	Euphoria	*	*	1.3	2.5	1.7	*
	Hallucination	*	*	8.9	2.5	1.4	*
	Illusion	-	-	1.3	-	-	-
	Insomnia	3.6	1.3	26.8	20.4	3.6	2.2
	Sleep disorder	-	-	12.1	8.3	*	*
Respiratory	Dyspnea	-	-	8.9	6.4	-	-
Skin and Appendages	Rash	-	-	10.2	4.5	-	-
Special Senses	Accommodation abnormal	-	-	8.3	6.4	-	-
Urinary	Micturition disorder	-	-	10.8	5.1	-	-

* an incidence of <1%
- the adverse event was not reported

Selegiline and mortality

In 1995, the UK Parkinson's Disease Research Group (PDRG) reported in a 5.6 year interim analysis of the long-term prospective study an increased overall mortality in the patient group randomised to receive selegiline and levodopa, when compared to those treated with levodopa only. This study has been the subject of considerable debate and criticism in the medical literature because of significant design and clinical research practice issues. A further 21 months update (mean 6.8 years) on the study including all mortality information to the end of September 1995 was published in 1998.

During 1996 to 1997, the British Medicines Control Agency (MCA) sponsored a study evaluating mortality among patients with Parkinson's disease on various treatments using data from their General Practice Research Database. This study, combined with the MCA's review of all available evidence from trials and observational studies, did not confirm the increased mortality risk in users of selegiline in combination with levodopa, which was seen in the PDRG study.

No other clinical trial to date has shown an increase in mortality associated with the use of selegiline. The need for a formal systematic review of all relevant trial data to assess survival, disability and the risk of dementia has been identified.

Post-marketing surveillance data

Adverse events experienced by patients on monotherapy or adjunctive therapy from spontaneous reports have not been separated.

The estimated frequency of adverse events for a body system, is listed below. Frequency has been grouped according to the following criteria:

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/1,000 and < 1/100

Rare ≥ 1/10,000 and < 1/1,000

Very rare < 1/10,000

Not known cannot be estimated form the available data

Psychiatric disorders	Common	Sleeping disorders, confusion, hallucinations.
	Uncommon	Aggressive reaction, anxiety, delirium, depression, insomnia, increased libido, manic reaction, nervousness, paranoid reaction, paroniria, psychosis, somnolence, abnormal thinking.
	Not known	Impulse control disorders and compulsions.
Nervous system disorders	Common	Dry mouth, abnormal movements (such as dyskinesias), vertigo, dizziness, headache.
	Rare	Agitation, headache, increased flushing and sweating, syncope, ataxia, coma, convulsions, dizziness, abnormal gait, hypertonia, involuntary muscle contractions, speech disorder, tremor, mild transient sleep disorder (such as insomnia).
	Very rare	Neuroleptic malignant syndrome.
Cardiovascular disorders	Common	Postural hypotension, bradycardia.
	Rare	Cardiac arrhythmias, angina pectoris, cerebrovascular disorder, hypertension, hypotension, myocardial infarction, palpitation, supraventricular tachycardia.
Vascular disorders	Rare	Postural hypotension
Haematological disorders	Very rare	White cell disorder, thrombocytopaenia.
General disorders	Rare	Asthenia, death, fatigue, fever, malaise, oedema, pain.
Gastrointestinal disorders	Common	Nausea
	Rare	Abdominal pain, anorexia, constipation, diarrhoea, dyspepsia, vomiting, dry mouth.
Hepato-biliary disorders	Common	Increased hepatic enzymes
Skin and subcutaneous tissue disorders	Rare	Skin reactions, alopecia, photosensitivity reactions, pruritus, rash.
Renal and urinary disorders	Rare	Micturition difficulties
Metabolic and nutritional disorders	Very rare	Hyperglycaemia, hypoglycaemia
Musculo-skeletal system disorders	Very rare	Muscular weakness
Reproductive disorders	Very rare	Sexual dysfunction
Respiratory system disorders	Very rare	Dyspnoea
Special senses disorders	Very rare	Taste perversion, tinnitus, abnormal vision

DOSAGE AND ADMINISTRATION

Selegiline is administered as monotherapy in the early phase of the disease, or as adjunctive therapy with levodopa (with/without a peripheral decarboxylase inhibitor). In each case the initial dose is 5 mg taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of adjunctive treatment, an attempt may be made to reduce the dose of levodopa (10 to 30%) if levodopa-related adverse reactions occur. During continued selegiline therapy, further reductions of levodopa may be possible.

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.

After the initiation of levodopa therapy, selegiline potentiates and extends the effect of levodopa, and thus a reduction of levodopa dosage is possible. By adding selegiline to levodopa therapy the fluctuations in disability, e.g. end-of-dose type fluctuations, can be reduced.

OVERDOSAGE

Overdoses have no specific clinical picture. 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 MAOIs (central nervous and cardiovascular system disorders). Symptoms of non-selective MAOIs overdosage can progress over 24 hours to include drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucination, tremor, alternating high and low 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 the treatment should be symptomatic.

No overdosage cases are known. 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.

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Selgene, Selegiline hydrochloride 5 mg tablet: round white tablet, debossed "SN/5" on one side, "G" on the other; available in blister packs* or bottles of 100 tablets.

* Not marketed in Australia

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

18/07/2003

DATE OF MOST RECENT AMENDMENT

01/04/2015

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