PRODUCT MONOGRAPH

TEVA-SELEGILINE

(Selegiline Hydrochloride)

5 mg Tablets

Teva Standard

Antiparkinsonian Agent

Teva Canada Limited
Toronto, Canada

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THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent

ACTION AND CLINICAL PHARMACOLOGY

TEVA-SELEGILINE (selegiline hydrochloride) is an irreversible inhibitor of the enzyme monoamine oxidase (MAO). Because selegiline has greater affinity for type B than type A MAO, it can serve as a selective inhibitor of MAO-B if it is administered at the recommended dose.

Selegiline may have pharmacological effects unrelated to MAO-B inhibition. There is some evidence that it may increase dopaminergic activity by interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principle metabolites, amphetamine and methamphetamine, have pharmacological actions of their own, they interfere with neuronal re-uptake and enhance the release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). The extent to which these neurotransmitters contribute to selegiline's effects are unknown.

Rationale for the use of selective MAO-B inhibitors in Parkinson's disease: Many of the prominent symptoms of Parkinson's Disease are due to deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic

neurons which originate in the substantia nigra and project to the striatum. Early in the course of the disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by the administration of exogenous levodopa. After several years of levodopa therapy, the response to a given dose of levodopa is often accompanied by side effects (dyskinesia, on-off phenomena, freezing).

MAO-B inhibitors may be useful under these conditions because by blocking the catabolism of dopamine, they increase the net amount of dopamine available. In patients with advanced Parkinson's Disease, the addition of selegiline to levodopa (usually with a decarboxylase inhibitor) has been shown to improve the therapeutic effect of levodopa.

Recently, in newly diagnosed patients, selegiline was shown to delay the need to implement levodopa therapy.

The mechanisms of action of selegiline, both in newly diagnosed and in severely incapacitated patients, is unknown.

Hypertensive Crisis ("Cheese Reaction")

The MAO's are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall and brain. In the intestine, type A is the predominant MAO; it is thought to provide vital protection from exogenous amines (e.g. tyramine) that have the capacity to displace norepinephrine from storage sites and thereby cause a hypertensive crisis ("cheese reaction"). MAO-A catabolises the exogenous amines which are found in a variety of foods (fermented cheese, red wine, herring) and drugs (over-the-counter cough/cold medications). Since MAO-A in the gut is not inhibited by therapeutic doses of selegiline, in theory, patients may take medications containing

pharmacologically active amines and consume tyramine-containing foods without the risk of uncontrolled hypertension.

To date, clinical experience confirms this and there have been no reports of hypertensive crises ("cheese reactions") in selegiline hydrochloride treated patients. However, until the pathophysiology of the "cheese reaction" is more completely understood, safe administration of TEVA-SELEGILINE without dietary restrictions should only be assumed at doses which presumably, selectively inhibit MAO-B (e.g., 10 mg/day). Hence, if TEVA-SELEGILINE is to be used without elaborate restrictions being placed on diet and concomitant drug use, close attention to the dose dependent nature of TEVA-SELEGILINE's selectivity is critical.

Pharmacokinetics

The extremely short half-life of selegiline (<0.15 hours following a 10 mg i.v. dose) is consistent with the inability to detect unchanged selegiline in the serum and urine following oral administration.

Presently, there is only preliminary information about the details of the pharmacokinetics of selegiline hydrochloride and its metabolites. In a 7-day study conducted to investigate the effect of selegiline on the pharmacokinetics of an oral hypoglycemic agent, subjects were given a 10 mg dose of selegiline hydrochloride. Serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Trough levels of the three metabolites were as follows: N-desmethylselegiline, the major metabolite was not detectable; the levels of amphetamine and methamphetamine were 3.5 ng/mL and 8.0 ng/mL respectively.

The rate of MAO-B regeneration following discontinuation of treatment has not yet been determined. It is this rate, dependent upon *de novo* protein synthesis, that probably determines how quickly normal MAO-B activity can be restored.

A comparative, single dose, two-way crossover bioavailability study was performed on two 5 mg selegiline tablet formulations, TEVA-SELEGILINE 5 mg tablets and Eldepryl® 5 mg tablets. The pharmacokinetic data calculated for a single oral dose of 2 X 5 mg tablets (selegiline tablet formulations TEVA-SELEGILINE versus Eldepryl®) under fasting conditions are tabulated :

Pharmacokinetic Indices for N-Desmethyl Selegiline:

Geometric Mean Arithmetic Mean (C.V.)			
	Teva-Selegiline (2X5 mg)	Eldepryl® (Deprenyl Research, Canada) (2X5 mg)	Percentage of Eldepryl®
AUC_T (ng•h/mL)	37.71 40.66 (45)	34.47 37.59 (42)	109
AUC_I (ng•h/mL)	38.86 42.08 (45)	35.87 38.92 (42)	108
C_{max} (ng/mL)	15.64 16.56 (33)	15.33 16.49 (38)	102
T_{max}* (h)	1.13 (0.72)	1.00 (0.38)	---
$T_{1/2}$* (h)	5.39 (3.36)	4.73 (2.56)	---

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

TEVA-SELEGILINE (selegiline hydrochloride) may be useful as an adjunct to levodopa (usually with a decarboxylase inhibitor) in the management of some patients with Parkinson's Disease; in newly diagnosed patients before symptoms begin to affect the

patient's social or professional life, at which time more efficacious treatment becomes necessary.

CONTRAINDICATIONS

TEVA-SELEGILINE (selegiline hydrochloride) is contraindicated in patients with a known hypersensitivity to this drug. Patients with active peptic ulcer or patients with other extrapyramidal disorders such as excessive tremor or tardive dyskinesia or patients with severe psychosis or profound dementia should not be administered TEVA-SELEGILINE. Combination of TEVA-SELEGILINE with meperidine is also contraindicated. This contraindication is often extended to other opioids as well.

WARNINGS

Selective Versus Non-Selective Inhibition of MAO-B

Because of the risks associated with non-selective inhibition of MAO, TEVA-SELEGILINE (selegiline hydrochloride) should not be used at daily doses exceeding those recommended (10 mg/day). (See ACTION AND CLINICAL PHARMACOLOGY). Even at the recommended daily dose of 10 mg/day, the selectivity of TEVA-SELEGILINE may not be absolute. Selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO has not yet been determined, but may be in the range of 30 to 40 mg/day.

Clinical data on the concomitant use of selegiline and fluoxetine hydrochloride are not available. Death has been reported to occur following the initiation of therapy with nonselective MAO inhibitors (phenelzine, tranylcypromine) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with selegiline; however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to

avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least 5 weeks (approximately 5 half-lives) should elapse between discontinuation of fluoxetine and initiation of MAO inhibitor therapy. Based on experience with the combined use of MAO inhibitors and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

PRECAUTIONS

General:

An exacerbation of levodopa-associated side effects, presumably due to the increased amounts of dopamine reacting with supersensitive post-synaptic receptors, may be experienced in some patients receiving TEVA-SELEGILINE (selegiline hydrochloride). Reducing the dose of levodopa by approximately 10 to 30% will often moderate these effects. The MAO system of enzymes is complex and not completely understood, and, since there is only a limited amount of carefully documented clinical experience with selegiline hydrochloride the decision to prescribe TEVA-SELEGILINE should take this into consideration. It is advisable, therefore, to observe the patients closely for atypical responses since the full spectrum of possible responses to selegiline hydrochloride may not have been observed in pre-marketing evaluation of the drug.

Warning to Patients

Patients should be advised that after initiation of TEVA-SELEGILINE, there may be a possible need to reduce levodopa dosage. The patients (or their families if the patient is incompetent) should be advised that the recommended daily dose of 10 mg should not be exceeded. A brief description of the "hypertensive crisis" ("cheese reaction") should be

provided and the risks of using higher daily doses of TEVA-SELEGILINE explained. Although hypertensive reactions have not been reported with selegiline hydrochloride, documented experience is limited. Therefore it may be beneficial to inform patients (or their families) about the signs and symptoms associated with MAO inhibitors induced hypertensive reactions. In particular, patients should be urged to immediately report any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests

No specific laboratory tests are considered essential for the management of patients on TEVA-SELEGILINE. In long-term therapy, transient or continuing abnormalities with tendency for elevated values in liver function tests have been described. Although serious hepatic toxicity has not been observed, caution should be exercised in patients with a history of hepatic dysfunction. Periodic routine evaluation of all patients is, however, appropriate.

Drug Interactions

The occurrence of stupor, muscular rigidity, severe agitation and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. Symptoms resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs.

Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination. While it cannot be said definitively that all of these reactions were caused by this combination, they are all compatible with this well recognized interaction.

Although the database of documented clinical experience is limited, MAO inhibitors are ordinarily contraindicated for use with meperidine. This warning is often extended to other opioids.

It is also prudent to avoid the concomitant use of TEVA-SELEGILINE and fluoxetine. (see WARNINGS)

Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (see WARNINGS and PRECAUTIONS).

Carcinogenesis

Studies conducted to determine the carcinogenic potential of selegiline hydrochloride have not been completed.

Use During Pregnancy

There have not been sufficient animal reproduction studies with selegiline hydrochloride to conclude that selegiline hydrochloride poses no teratogenic potential. However, one study in rats at doses 180 fold the recommended human doses revealed no evidence of teratogenic effect. Whether or not selegiline hydrochloride can cause fetal harm when administered to a pregnant woman or whether reproductive capacity is affected is not yet known. TEVA-SELEGILINE should only be administered to a pregnant woman only if it is clearly necessary and the benefit versus risk must be evaluated carefully.

Nursing Mothers

It is not known whether TEVA-SELEGILINE is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all, except those which are absolutely necessary, drug treatments in nursing women.

Pediatric Use

The safety and effects of TEVA-SELEGILINE in children have not been evaluated.

ADVERSE REACTIONS

The side effects reported with use of selegiline hydrochloride are usually those associated with excessive dopaminergic stimulation. The side effects of levodopa may be potentiated by the use of the drug. Therefore, adjustment of drug dosages may be necessary. When selegiline hydrochloride has been used as an adjunct to levodopa therapy, some of the more serious adverse reactions reported were hallucinations and confusion, particularly visual hallucinations.

Although a cause and effect relationship has not been established, after long-term therapy, a tendency to a progressive use in several liver enzymes has been observed.

The following adverse effects, in decreasing order of frequency led to discontinuation of treatment of selegiline hydrochloride in prospective clinical trials: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased abnormal involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only rarely which caused discontinuation are ankle edema, anxiety, burning lips/mouth, constipation,

drowsiness/lethargy, dystonia, excess perspiration, increase of episodes of freezing, gastrointestinal bleeding, hair loss, increasing tremor, nervousness, weakness and weight loss.

The following adverse reactions were reported in controlled clinical trials involving a very limited number of patients (N=49 receiving selegiline hydrochloride; N=50 receiving placebo). (Incidences are devoid of practical statistical significance.):

A. IN COMBINATION WITH LEVODOPA

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS IN CLINICAL TRIAL

ADVERSE EVENT	Number of Patients	
	ELDEPRYL	PLACEBO
Nausea	10	3
Dizziness/Lightheaded/Faintness	7	1
Abdominal pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid dreams	2	0
Dyskinesias	2	5
Headache	2	1
Ache, generalized	1	0
Anxiety/tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary retention	1	0
Weight loss	1	0

B. IN MONOTHERAPY

The incidence of adverse reactions occurring in trials using selegiline hydrochloride as monotherapy has not been fully reported to date. Serious adverse reactions were as follows: Depression, chest pain, myopathy and diarrhea. Other reported adverse reactions included insomnia, headache, nausea, dizziness and vertigo.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System

Motor/Coordination/Extrapyramidal: Increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch, myoclonic jerks, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioural/Psychiatric: Hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behaviour/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory, increased energy, transient high, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: Headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System

Dry mouth, blurred vision, sexual dysfunction.

Cardiovascular

Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal

Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism.

Genitourinary/Gynecologic/Endocrine

Transient anorgasmia, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation, urinary frequency.

Skin and Appendages

Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous

Asthma, diplopia, shortness of breath, speech affected.

Toxic delirium has also been reported with selegiline hydrochloride when used as adjunctive therapy to levodopa treatment

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific information available regarding clinically significant overdoses with selegiline hydrochloride. However, during the development of selegiline hydrochloride, it was revealed that some individuals exposed to doses of 600 mg/day of selegiline hydrochloride suffered severe hypotension and psychomotor agitation. Overdoses are

likely to cause significant inhibition of both MAO-A and MAO-B, since the selective inhibition of MAO-B by selegiline is achieved only at doses recommended for the treatment of Parkinson's Disease (i.e., 10 mg/day). Consequently, the signs and symptoms of overdose with selegiline hydrochloride may resemble those observed with marketed non-selective MAO inhibitors (e.g., tranylcypromine, isocarboxazide and phenelzine).

Characteristically, with non-selective MAO inhibitors, signs and symptoms may not appear immediately. There may be delays of up to 12 hours from the time of ingestion of the drug and the appearance of signs. Following the overdose, the peak intensity of the syndrome may not be reached for upwards of a day. Following overdosage with non-selective MAO inhibitors, death has been reported. Therefore, immediate hospitalization with continuous patient observation and monitoring is strongly recommended. The clinical picture of MAO inhibitor overdose varies considerably; its severity may be related to the amount of drug consumed. The central nervous system and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis and cool clammy skin.

Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Provided the airway has been protected against aspiration, induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning. Signs and symptoms of central system stimulation, including convulsions, should be treated with

diazepam, given slowly intravenously. Central nervous system stimulants and phenothiazine derivatives should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with a dilute pressor agent infused intravenously. It should be noted that a markedly increased pressor response may be produced by adrenergic agents. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanically supported ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION

The recommended dosage of TEVA-SELEGILINE (selegiline hydrochloride) as monotherapy in newly diagnosed patients, or as an adjunct to levodopa (usually with a decarboxylase inhibitor) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch.

The recommended dosage of TEVA-SELEGILINE (selegiline hydrochloride) as an adjunct in the management of patients with Parkinson's Disease is 10 mg/day administered as divided doses of 5 mg each taken at breakfast and lunch. When TEVA-SELEGILINE adjunctive therapy is added to the existing levodopa therapeutic regime, a reduction, usually of 10 to 30% in the dose of levodopa (in some instances a reduction of dose of TEVA-SELEGILINE to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects.

Doses higher than 10 mg/day should not be used. There is no evidence that additional benefit will be obtained from the administration of higher doses. The dose of 10 mg/day results in an almost complete selective inhibition of MAO-B enzyme. The inhibitory action of TEVA-SELEGILINE is irreversible, the duration of drug effect depends on enzyme regeneration. Higher doses will result in a loss of selectivity of TEVA-SELEGILINE towards MAO-B with an increase in the inhibition of type MAO-A. Moreover, there is an increased risk of adverse reactions with higher doses as well as an increased risk of the "cheese reaction" with its hypertensive response.

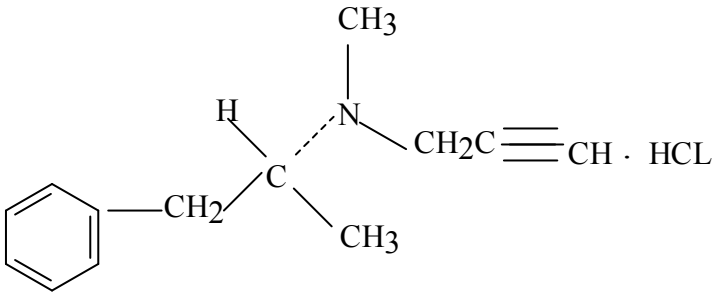
PHARMACEUTICAL INFORMATION

Trade Name: TEVA-SELEGILINE

Proper Name: Selegiline Hydrochloride

Chemical Name: (–)-(R)-N, a-Dimethyl-N-2-propynylphenethylamine hydrochloride

Structural Formula:



Molecular Formula: $C_{13}H_{17}N \cdot HCl$ Molecular Weight: 223.75

Description: Selegiline hydrochloride is a white crystalline odourless powder, freely soluble in water, chloroform and methanol. The melting range is between 141 and 144^{0}C.

Composition: Lactose, corn starch, povidone, magnesium stearate, talc, water.

Stability and Storage Recommendations: Store bottles between 15-25 ^{0}C and protect from high humidity in well-closed, light resistant containers. Store unit dose boxes between 15^{0}-25^{0}C and protect from light.

AVAILABILITY

TEVA-SELEGILINE (selegiline hydrochloride) is available as:

5 mg white to off-white, round, flat face, bevelled edge, compressed tablet, engraved 'novo' on one side and '5' on the other side.

Supplied: Bottles of 60, 100, 300, 500, 1000 and unit dose boxes of 100.

PHARMACOLOGY

Pharmacodynamics

At therapeutic doses (10 mg orally per day), selegiline is a potent and selective inhibitor of monoamine oxidase Type B (MAO-B), the enzyme predominantly responsible for the metabolism of dopamine in the human brain. The effect of selegiline on this enzyme is irreversible. Because selegiline irreversibly inhibits MAO-B, its duration of effect is mainly dependent upon enzyme regeneration. Selectivity may be lost at doses higher than the recommended therapeutic dose and partial inhibition of MAO-A may occur.

Selegiline also inhibits the uptake of monoamines (dopamine, tyramine, noradrenaline) into the nerve endings of catecholaminergic neurons, independent of its inhibitory action on MAO-B. These two modes of action have a net result of an increased concentration of dopamine in the brain. Selegiline, thus, increases the "bioavailability" of levodopa. As a result, the dose of levodopa necessary for the treatment of Parkinson patients can be

reduced (by 10-30% on the average), while maintaining optimal therapeutic response. The incidence and severity of side effects decreases as a result of the reduction in the daily levodopa dosage, frequently below that associated with the initial levodopa therapy. Ten mg/day is the recommended effective dose of selegiline for potentiating the antiparkinson effects of levodopa therapy. Increases in the daily dosage beyond this level do not achieve enhanced efficacy. Selegiline is metabolized to l-desmethylselegiline, l-methamphetamine and l-amphetamine, however, these metabolites do not contribute significantly to the therapeutic efficacy of the drug.

Selegiline does not affect the activity of MAO-A, the predominant enzyme in the gut, at the recommended therapeutic dose. Therefore, selegiline is devoid of the "hypertensive crisis" ("cheese reaction"). During long-term (2-8 years) daily administration of the drug, neither hypertensive reactions nor the need for any special dietary restrictions were ever encountered. It was concluded from a retrospective analysis of patients treated with long-term chronic selegiline treatments that there is a statistically significant increase in the life span (by approximately 15 months) of Parkinsonian patients when selegiline is added to their existing therapeutic regimen. The data suggest that the degeneration of the dopaminergic nigrostriatal system may actually be suppressed by the drug to some extent, thereby altering the course of the disease. Animal studies where it has been shown that the parkinson-like symptoms resulting from MPTP-induced lesions of the caudate nucleus can be prevented by the selective MAO-B inhibitors, support this observation.

Pharmacokinetics

Radiotracer studies in animals show that selegiline is rapidly and completely absorbed after oral administration, and is extensively metabolized. In animals, elimination of selegiline and its metabolites is virtually complete within a day. In humans, selegiline is

highly bound to plasma protein (94% *in vitro*), but, following single or multiple oral doses (steady state) of 5-10 mg selegiline plasma levels of the unchanged drug are not detectable (<1% of the dose administered).

Since selegiline is a lipophilic substance it rapidly crosses the blood/brain barrier. It was determined from studies in blood platelets, that contain only MAO-B, MAO-B inhibition in man exhibits non-linear kinetics. This conclusion is attributed to the fact that the inhibitory effect of selegiline on MAO-B is irreversible and dissipates only through enzyme resynthesis.

The major metabolites of selegiline are l-amphetamine, l-methamphetamine and N-desmethylselegiline. A single dose and steady state pharmacokinetic study was conducted following the oral administration of 5-10 mg selegiline in healthy fasting volunteers. Unchanged selegiline could not be detected in either the serum or urine samples under these conditions (the limit of detection of the HPLC method utilized in these studies was 10 ng/mL). The half-life for N-desmethylselegiline was relatively short ($t_{1/2}$ = 2.1 hours), whereas that for l-amphetamine and l-methamphetamine was 17.7 and 20.5 hours, respectively. Forty-eight hours after the administration of the drug, these three metabolites accounted for 45% of the dose. Amphetamines may be present in the brain at concentrations equivalent to those found after a dose of 10 to 20 mg of methamphetamine, after long-term selegiline treatment. Adverse effects such as withdrawal symptoms or drug dependency have not been observed, since the metabolites are the l-isomers, which are 2-3 times less pharmacologically active than the d-isomers. Parkinson patients receiving selegiline exhibit 24-hour urine excretions of amphetamine and methamphetamine ranging from 0.45 to 1.63 mg (mean of 1.1 mg) and 1.45 to 4.03 (mean of 2.5), respectively, with less than 6.5% of the S(+)-isomer being present in any of the

samples. Approximately 50% of selegiline is apparently metabolized to amphetamine by conversion from methamphetamine.

Post-mortem examination of the brains of Parkinson patients treated with selegiline have shown that chronic treatment with 10 mg/day results in the inhibition of dopamine oxidation by up to 85-90%, 48 hours after the last dose of selegiline. Serotonin oxidation, on the other hand, was inhibited by only 65% maximum, which, in turn, did not affect the 5 HIAA concentrations in the brain.

A half-life of 0.15 hours for unchanged selegiline was obtained following the intravenous administration of 10 mg selegiline. The half-life of N-desmethylselegiline was approximately the same as that found after oral administration (2.7 vs. 2.1 hours). After 3 hours there was no unchanged selegiline found in the serum. The extremely short half-life of selegiline is consistent with inability to detect unchanged selegiline in the serum and urine following oral administration.

TOXICOLOGY

The results of the acute toxicity, chronic toxicity and reproductive/teratologic studies as well as the calculated therapeutic ratio, based on a recommended human dose of 10 mg/day, equivalent to 0.14 mg/kg/day for a 70 kg individual, are presented in Tables 1, 2, 3, respectively.

Acute Toxicity

Acute toxicity studies did not reveal any specific target organs of toxicity.

Table 1

LD50 Values From Acute Toxicity Studies with Selegiline HCl and Calculation of the Therapeutic Ratio

Species	Route	Sex	LD_{50} (mg/kg)	Confidence Limits or Minimum Lethal Dose	Therapeutic Range**
Rat	p.o.*	M	422	333-535	3014
	p.o.*	F	303	228-407	2161
	s.c.*	M	146	110-194	1044
	s.c.*	F	112	89-142	802
	i.v.	M	75	67-84	539
	i.v.	F	70	62-79	499
Mouse	p.o.*	M	445	363-546	3181
	p.o.*	F	365	288-464	2609
	s.c.*	M	205	162-262	1471
	s.c.*	F	190	152-237	1357
	i.v.	M	50	42-58	356
	i.v.	F	51	41-62	361
Dog	p.o.	M/F	~200		1429

*Subsequent observation period 24Ð168 hours

**With respect to 0.14 mg/kg/day/patient

Long-term Toxicity

In both rats and in dogs, long-term toxicity studies showed dose-dependent, amphetamine-like symptoms. Reduction in appetite and other pharmacodynamic actions caused only reversible effects and were observed at such doses that a safety factor of 21 to 36 exists between the "no-toxic-effect" dose of 3-5 mg/kg and the prospective human dose. There was no morphological evidence of organ damage. These results must be interpreted with caution in view of methodological problems with some of these studies.

Table 2

Determination of Non-Toxic Doses of Selegiline HCl and of the Therapeutic Range From Preclinical Toxicity Studies with Repeated Oral Administration**

Species	Duration	Dose (mg/kg)	#Animals per Group	No Toxic Dose	Therapeutic Range**
Rat	2 Weeks	0-80	20/20	-	-
	4 Weeks	0-270	8/8	10	71
	6 Months	0-30	20/20	30	214
	6 Months	0-90	10/10	10	71
Dog*	6 Months	0-30	7/7	3-10	
Dog	6 Months	0-20	2/2	5	36

* - with recovery period

** - with respect to 0.14 mg/kg/day/patient

Reproduction and Teratology

Reproduction studies in rats and rabbits revealed no teratogenic potential of selegiline and fertility studies in rats showed no effect at doses up to 100 mg/kg. In studies on peri- and post-natal development, toxic effects were observed primarily in the mothers and secondarily in the fetuses and neonates. These effects were attributed to the excessive

pharmacodynamic action of doses of 16 mg/kg and higher. In these studies a no-toxic-effect level of 4 mg/kg was established.

Table 3

Effect-Free Doses of Selegiline HCl from Reproduction Toxicity Studies and Calculation of the Therapeutic Range*

Species	Segment	Dose mg/kg	Effect-Free Dose	Range
Rat	I**	25		
(fertility)		50		
teratology		100	100	715
reproduction				
Rat	II	4		
(teratology)		12		
		36	4	30
Rabbit	II	0		
		25		
		50		
		100	100	715
Rat	III	0		
Perinatal		4		
Postnatal		16		
		64	4	29

* With respect to 0.14 mg/kg/day/patient

** Modified test design, no treatment from 1st-6th day post conception

Mutagenicity and Carcinogenicity

Selegiline did not demonstrate any mutagenic potential in a number of tests on gene and chromosone mutations in prokaryotic and eukaryotic cells as well as in cell culture and *in vivo*. Also, no effects on DNA or induction of cell transformation processes which might form the basis of carcinogenic activity, were observed.

REFERENCES

1. Birkmayer W, Knoll J, Riederer P, Youdim MBH. (-)-Deprenyl leads to prolongation of L-dopa efficacy in Parkinson's disease. Mod Probl Pharmacopsychiat 1983; 19: 170-6.

2. Birkmayer W, Knoll J, Riederer P, et al. Increased life expectancy resulting from addition of L-deprenyl to Madopar® treatment in Parkinson's disease: a longterm study. J Neural Transm 1985; 64: 113-27.

3. Boyson SJ. Psychiatric effects of selegiline. Arch Neurol 1991; 48: 902.

4. Brodersen P, Philbert A, Gulliksen G, Stigard A. The effect of L-deprenyl on on-off phenomena in Parkinson's disease. Acta Neurol Scand 1985; 71: 494-7.

5. Chiba K, Trevor A, Castagnoli N. Metabolism of the neurotoxic tertiary amine, MPTP, by brain monoamine oxidase. Biochem Biophys Res Commun 1984; 120: 574-8.

6. Cohen G, Pasik P, Cohen B et al. Pargyline and deprenyl prevent the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys. Eur J Pharmacol 1984; 106: 209-10.

7. Elsworth JD, Glover V, Reynolds GP et al. Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the "cheese effect". Psychopharmacology 1978; 57: 33-8.

8. Elsworth JD, Sandler M, Lees AJ et al. The contribution of amphetamine metabolites of (-)-deprenyl to its antiparkinsonian properties. J Neural Transm 1982; 54: 105-10.

9. Gerstenbrand F, Ransmayr G, Poewe W. Deprenyl (selegiline) in combination treatment of Parkinson's disease. Acta Neurol Scand 1983; Suppl. 95: 123-6.

10. Golbe LI, Langston JW, Shoulson I. Selegiline and Parkinson's disease. Protective and symptomatic considerations. Drugs 1990; 39: 646-51.

11. Golbe LI, Lieberman AN, Muenter MD et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. Clin Neuropharmacol 1988; 11: 45-55.

12. Heinonen EH, Myllyla V, Sotaniemi K, et al. Pharmacokinetics and metabolism of selegiline. Acta Neurol Scand 1989; 126:93-9.

13. Heinonen EH, Rinne UK, Tuominen J. Selegiline in the treatment of daily fluctuations in disability of parkinsonian patients with longterm levodopa treatment. Acta Neurol Scand 1989; 126: 113-8.

14. Karoum F, Chuang LW, Eisler T et al. Metabolism of (-) deprenyl to amphetamine and methamphetamine may be responsible for deprenyl's therapeutic benefit: a biochemical assessment. Neurology 1982; 32: 503-9.

15. Knoll J. The possible mechanism of action of (-) deprenyl in Parkinson's disease. J Neural Transm 1978; 43: 177-98.

16. Knoll J, Magyar K. Some puzzling pharmacological effects of monoamine oxidase inhibitors. Adv Biochem Psychopharmacol 1972; 5: 393-408.

17. Lieberman AN, Gopinathan G, Neophytides A, Foo SH. Deprenyl versus placebo in Parkinson disease: a double-blind study. NY State J Med 1987; 87: 646-9.

18. Magyar K, Tothfalusi L. Pharmacokinetic aspects of deprenyl effects. Pol J Pharmcol Pharm 1984; 36: 373-84.

19. Presthus J, Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. Acta Neurol Scand 1983; Suppl. 95: 127-33.

20. Reynolds GP, Elsworth JD, Blau K et al. Deprenyl is metabolized to methamphetamine and amphetamine in man. Br J Clin Pharmac 1978; 6: 542-4.

21. Riederer P, Youdim MBH. Monoamine oxidase activity and monoamine metabolism in brains of parkinsonian patients treated with l-deprenyl. J Neurochem 1986; 46: 1359-65.

22. Riederer P, Youdim MBH, Rausch WD et al. On the mode of action of l-deprenyl in the human central nervous system. J Neural Transm 1978; 43: 217-26.

23. Rinne UK. Deprenyl (selegiline) in the treatment of Parkinson's disease. Acta Neurol Scand 1983; Suppl. 95: 107-11.

24. Sivertsen B, Dupont E, Mikkelsen P et al. Selegiline and levodopa in early or moderately advanced Parkinson's disease: a double-blind controlled short- and long-term study. Acta Neurol Scand 1989; 126: 147-52.

25. Yoshida T, Yamada Y, Yamamoto T, Kuroiwa Y. Metabolism of deprenyl, a selective monoamine oxidase (MAO) B inhibitor in rat: relationship of metabolism to MAOÐB inhibiting potency. Xenobiotica 1986; 16: 129-36.

26. CPS 26th Edition Compendium of Pharmaceuticals and Specialties 1991. Canadian Pharmaceutical Association, Ottawa, Ont. pp. 421-3.

27. PDR 45th Edition. Physician's Desk Reference. 1991. Oradell, NJ, USA. pp. 2133-4.

28. United States Food and Drug Administration Summary Basis for Approval Documents for Approval NDA 19-334. USA.

29. Product Monograph for Eldepryl® (selegiline hydrochloride). July 12, 1990. Revised August 26, 1993. Deprenyl Research Ltd. Toronto, Ont.