PRODUCT MONOGRAPH

MYLAN-SELEGILINE
(selegiline hydrochloride)

5 mg Tablets

Antiparkinsonian Agent

Mylan Pharmaceuticals ULC
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(selegiline hydrochloride)

Tablets - 5 mg

THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent

CLINICAL PHARMACOLOGY

Selegiline hydrochloride, previously known as l-deprenyl hydrochloride, a synthetic selective inhibitor of the MAO-B enzyme when administered at the recommended doses, has been found to be of value as an adjunct to the management of some patients with Parkinson's Disease when administered as add-on therapy to levodopa/carbidopa. The mechanism of action of selegiline hydrochloride responsible for its action as an adjunct in the symptomatic management of selected Parkinsonian patients is not well understood. Inhibitors of type MAO-B enzyme may be useful by blocking the metabolism of dopamine and by increasing the net amount of dopamine available. It may increase dopaminergic activity by blocking dopamine uptake at the synapses. Two principal metabolites of selegiline hydrochloride, l-amphetamine and l-metamphetamine (which with l-desmethylselegiline account for 44% of dose administered, as excreted metabolites) could also play a role. They interfere with neuronal uptake. By inhibiting MAO-B enzyme, selegiline hydrochloride may prevent the generation of free radicals and hydrogen peroxide resulting from oxidation of dopamine. It may also prevent the conversion of MPTP to MPP. Non-selective

inhibitors of MAOs which inhibit MAO-A enzymes are not used in the management of Parkinson patients because of side effects, such as hypertension, increase in involuntary movements and toxic delirium. Toxic delirium has also been reported with selegiline hydrochloride when used as adjunctive therapy to levodopa treatment.

Hypertensive Crisis ("Cheese Reaction").

The MAOs are currently subclassified into two types, A and B, which differ in their substrates specificity and tissue distribution. In humans, intestinal MAO is predominantly MAO-A while most of that in the brain is MAO-B. In the CNS, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. The MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. The MAO-A found in the liver and the gastrointestinal tract is thought to provide vital protection from exogenous amines (e.g. tyramine) that have the capacity, if absorbed intact, to cause a "hypertensive crisis", the so-called "cheese reaction" (if large amounts of certain exogenous amines -e.g. from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc. - gain access to the systemic circulation, they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. The subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.) In theory, therefore, patients treated with selegiline hydrochloride at a dose of 10 mg a day, because gut MAO-A is not inhibited, can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. To date, clinical experience appears to confirm this prediction: hypertensive crises ("cheese reactions") have not been reported in selegiline

hydrochloride treated patients. However, until the pathophysiology of the "hypertensive crisis" is more completely understood, it seems prudent to assume that selegiline hydrochloride can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g. 10 mg/day). Hence, attention to the dose dependent nature of selegiline hydrochloride selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use (See WARNINGS and PRECAUTIONS).

Pharmacokinetics

A comparative, bioavailability study was conducted to compare the rate and extent of absorption of MYLAN-SELEGILINE 5 mg tablets against the Canadian Reference selegiline hydrochloride 5 mg tablets. The pharmacokinetic data calculated for the metabolite desmethylselegiline for MYLAN-SELEGILINE and Canadian Reference Product are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
DESMETHYLSELEGILINE (2 X 5 mg)
From measured and log-transformed data

Geometric Mean **Arithmetic Mean (CV%)**			
	Mylan-Selegiline	Eldepryl®**	% RATIO OF GEOMETRIC MEANS
AUC_T (xg.hr/mL)	34957.89 37254.4 (39.8%)	34713.62 37537.3 (46.6%)	 100.7
AUC_I (xg.hr/mL)	36892.6 39524.8 (42.4%)	36527.0 39832.7 (50.1%)	 101.1
C_{max} (xg/mL)	17354.415 17843.44 (23.9%)	16219.934 1640.31 (28.2%)	 107.0
T_{max} * (h)	0.8736 (31.8%)	0.9317 (37.4%)	--- ---
$T_{½}$ * (h)	3.893 (35.1%)	3.736 (28.7%)	--- ---

* The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means (CV%) only.

** Eldepryl®, manufactured by Draxis Health, Canada

Only preliminary information about the details of the pharmacokinetics of selegiline hydrochloride and its metabolites is available. Data obtained in a study of 12 healthy subjects that was intended to study the effects of selegiline hydrochloride on the pharmacokinetics of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline hydrochloride were below the limit of detection (less than 10 ng/ml). Three metabolites, N-desmethylselegiline, the major metabolite (mean half-life 2.0 hours), l-amphetamine (mean half-life 17.7 hours) and l-methamphetamine (mean half-life 20.5 hours) were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these three metabolites. In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough levels were 3.5 ng/ml for l-amphetamine and 8.0 ng/ml for l-methamphetamine, and those for N-desmethylselegiline were below the levels of detection. The rate of MAO-B regeneration following discontinuation of treatment has not been quantitated. It is this rate, dependent upon de novo protein synthesis, which seems likely to determine how fast normal MAO-B activity can be restored.

INDICATIONS AND CLINICAL USE

MYLAN-SELEGILINE (selegiline hydrochloride) may be of value:

- as an adjunct to levodopa (with or without a decarboxylase inhibitor) in the management of the signs and symptoms of Parkinson's disease.

- in newly diagnose patients before symptoms begin to affect the patient's social or professional life, at which time more efficacious treatment becomes necessary.

CONTRAINDICATIONS

MYLAN-SELEGILINE (selegiline hydrochloride) is contraindicated in patients with known hypersensitivity to this drug. MYLAN-SELEGILINE should not be used in patients with active peptic ulcer, in patients with other extrapyramidal disorders such as excessive tremor or tardive dyskinesia, or in patients with severe psychosis or profound dementia.

MYLAN-SELEGILINE is contraindicated in combination with meperidine, (see DRUG INTERACTIONS). This contraindications is often extended to other opioids as well.

WARNINGS

MYLAN-SELEGILINE (selegiline hydrochloride) should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO (see CLINICAL PHARMACOLOGY).

The selectivity of selegiline hydrochloride for MAO-B may not be absolute even at the recommended daily dose of 10 mg/day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline hydrochloride becomes a non-selective inhibitor of all MAO is unknown. Doses in the range of 30 to 40 mg a day are known to be non-selective. Because of reports of fatal interactions, MAO inhibitors are ordinarily contraindicated for use with

meperidine. This warning is often extended to other opioids. Because the mechanism of interaction between MAO inhibitors and meperidine is unknown, it seems prudent, in general to avoid this combination.

Serious CNS adverse events might occure when MYLAN-SELEGILINE is combined with tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs).

Hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non selective monoamine oxydase inhibitors (MAOIs) such as Nardil and Parnate. Similarly, the combined use of tricyclic antidepressants and MYLAN-SELEGILINE has been associated with hyperpyrexia, tremors, agitation, restlessness, reduced level of consciousness and in rare instances fatalities. Related adverse events also seen after this combination included hypertension, syncope, asystole, diaphoresis, seizure, change in behaviuoural and mental status, and muscular rigidity.

Serious, sometimes fatal, reactions with sighs andsymptoms than may include hyperthermia, tigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes than include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride (PROZAC) and non selective MAOIs. Similar signs have been reported in some patients on the combination of MYLAN-SELEGILINE (10 mg a day) and selective serotonin re-uptake inhibitors includine fluoxetine, sertraline and paroxetine.

Since the mechanixms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of MYLAN-SELEGILINE and tricyclic antidepressants as well as MYLAN-SELEGILINE and selective serotonin re-uptake inhibitors. At least 14 days should elapse between discontinuation of MYLAN-SELEGILINE and initiation of treatment with a tricyclic antidepressants or selective serotonin re-uptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prscribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatement with MYLAN-SELEGILINE.

PRECAUTIONS

General

Some patients given selegiline hydrochloride may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with supersensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%. The decision to prescribe MYLAN-SELEGILINE (selegiline hydrochloride) should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline hydrochloride. Consequently the spectrum of possible responses to selegiline hydrochloride may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe the patients closely for atypical responses.

Selegiline hydrochloride stimulates H-2 receptors in the stomach. It should be used cautiously in patients with existing peptic ulcers. At high doses (30 to 40 mg), selegiline hydrochloride begins to show inhibitory effect on MAO-A. At these doses hypertensive effects from tyramine are experienced.

Information for Patients

Patients should be advised of the possible need to reduce levodopa/carbidopa dosage after the initiation of MYLAN-SELEGILINE therapy. The patients (or their families if the patient is incompetent) should be advised not to exceed the recommended daily dose of 10 mg. The risk of using higher daily doses of MYLAN-SELEGILINE should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided. While hypertensive reactions with selegiline hydrochloride have not been reported, documented experience is limited. Consequently, it may be useful 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 report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests

No specific laboratory tests are deemed essential for the management of patients on selegiline hydrochloride. Transient or continuing abnormalities with tendency for elevated values in liver function test have been described in long term therapy. Although serious hepatic toxicity has not

been observed, caution is recommended 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, 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 (see CONTRAINDICATIONS).

It is also prudent to avoid the concomitant use of MYLAN-SELEGILINE and selective serotonin re-uptake inhibitors and tricyclic antidepressants (see WARNINGS).

Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of Mylan-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 to evaluate the carcinogenic potential of selegiline hydrochloride have not been completed.

Use during Pregnancy

Insufficient animal reproduction studies with selegiline hydrochloride have been done to conclude that selegiline hydrochloride poses no teratogenic potential. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline hydrochloride should be given to a pregnant woman only if clearly needed, and the benefit versus risk must be evaluated carefully.

Nursing Mothers

It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use

The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS

Introduction

The side effects of MYLAN-SELEGILINE (selegiline hydrochloride) are usually those associated wtih excessive dopaminergic stimulation. The drug may potentiate the side effects of levodopa,

therefore, adjustment of drug dosages may be required. Some of the most serious adverse reactions reported with the combination of MYLAN-SELEGILINE and levodopa were hallucinations and confusion, particularly visual hallucinations.

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

In prospective clinical trials, the following adverse effects, (listed in decreasing order of frequency), led to the DISCONTINUATION of MYLAN-SELEGILINE: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope.

Events reported only rarely as a cause of discontinuation of treatment include anxiety, drowsiness/lethargy, nervousness, dystonia, increased episodes of freezing, increased tremor, weakness, excessive perspiration, constipation, weight loss, burning lips/mouth, ankle edema, gastrointestinal bleeding and hair loss.

In controlled clinical trials involving a very limited number of patients (N= 49 receiving MYLAN-SELEGILINE; N=50 receiving placebo) the following adverse reactions were reported (incidences are devoid of practical statistical significance):

INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS IN CLINICAL TRIAL		
A. IN COMBINATION WITH LEVODOPA		
	Number of Patients Reporting Events	
ADVERSE EVENT	SELEGILINE HCl	PLACEBO
Nausea	10	3
Dizziness, lightheaded, faint	7	1
Abdominal pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid dreams	2	0
Dyskenesias	2	5
Headache	2	1
Ache, generalized	1	0
Anxiety/tension	1	1
Anaemia	0	1
Diarrhoea	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. Monotherapy

The incidence of adverse reactions occurring in trials using Selegiline 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/Co-ordination/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, insomnia, tiredness, delusions, disorientation, light-headedness, 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, hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal:

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

Genitourinary/Gynaecologic/Endocrine:

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

Skin and Appendages:

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

Miscellaneous:

Asthma, diplopia, shortness of breath, speech affected.

Toxic delirium has also been reported with Selegiline when used as adjunctive therapy to levodopa treatment.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during the development of selegiline hydrochloride reveals that some individuals exposed to doses of 600 mg/day of selegiline hydrochloride suffered severe hypotension and psychomotor agitation. Since the selective inhibition of MAO-B by selegiline hydrochloride is achieved only at doses recommended for the treatment of Parkinson's Disease (i.e. 10 mg per day), overdoses are likely to cause significant inhibition of both MAO-A and MAO-B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g. tranylcypromine (Parnate), isocarboxazide (Marplan), and phenelzene (Nardil)].

Overdose with non-selective MAO inhibitors:

Note: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of overdose with non-selective MAO inhibitors may not appear immediately. Delays of up to 12 hours between ingestion of the drug and the appearance of signs may occur. Importantly, 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 following overdose. 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 a function of 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, opisthotonos, 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:

Because there is no recorded experience with selegiline overdose, the following suggestions, based on the management of non-selective MAO inhibitor poisoning, might be applicable.

Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulation, including convulsions, should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response. 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 MYLAN-SELEGILINE (selegiline hydrochloride) as monotherapy in newly diagnosed patients, or as an adjunct to levodopa in the management of patients with Parkinson's Disease is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch.

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. Higher doses will result in a loss of selectivity of selegiline hydrochloride 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.

When selegiline hydrochloride adjunctive therapy is added to the existing levodopa/carbidopa therapeutic regime, a reduction, usually of 10 to 30% in the dose of levodopa/carbidopa (in some instances a reduction of dose of selegiline hydrochloride to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects.

PHARMACEUTICAL INFORMATION

Drug Substance

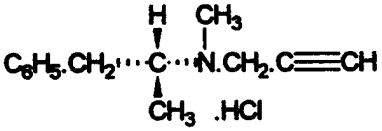
Proper Name: Selegiline hydrochloride

Chemical Name:

1) Benzeneethanamine, Ņ,-Demethyl-N-2propynyl-, hydrochloride, (R)

2) (-)-(R)-N, -Dimethyl-N-2-propynyl-phenethylamine hydrochloride

Structural Formula:



Empirical Formula: $C_{13}H_{17}N$ HCl

Molecular Weight: 223.75

Description: White to near white crystalline powder, freely soluble in water, chloroform and methanol.

pH: 3.5 - 4.5 (2% aqueous solution) .

Melting Point: 140-143°C

Composition: non-medicinal ingredients are: - Lactose, Maize Starch, Citric Acid, Povidone, Talc, and Magnesium Stearate.

Stability and Storage Recommendations: Store at room temperature between 15 and 30°C.

AVAILABILITY OF DOSAGE FORMS

MYLAN-SELEGILINE (selegiline HCl) 5 mg tablet contains 5 mg of the l-isomer of selegiline HCl (formerly l-deprenyl HCl). Each white tablets is 7.0 mm flat bevelled edged embossed "SE/5" on one side and "G" on the reverse side. Available in bottles of 60s.

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; its effect on this enzyme is irreversible. Because selegiline hydrochloride is an irreversible inhibitor of MAO-B, its duration of effect is mainly dependent upon enzyme regeneration. At doses higher than the recommended therapeutic dose, selectivity may be lost and partial inhibition of MAO-A may occur.

Independent of its inhibitory action on MAO-B, selegiline hydrochloride also inhibits the uptake of monoamines (dopamine, tyramine, noradrenaline) into the nerve endings of catecholaminergic neurons. The net result of these two modes of action is an increased concentration of dopamine in the brain. The "bioavailability" of levodopa is thus increased by selegiline hydrochloride. As a consequence the amount of levodopa required in the treatment of Parkinson patients can be reduced (by 10 - 30% on the average), while maintaining optimal therapeutic response. Reduction in the daily levodopa dosage also results in a decreased incidence and severity of side effects, frequently below that associated with the initial levodopa therapy. The recommended effective dose of selegiline for potentiating the antiparkinson effects of levodopa therapy is 10 mg per day. Enhanced efficacy is not achieved by further increases in the daily dosage beyond this level. Although selegiline is metabolized to l-desmethylselegiline, l-methamphetamine and l-amphetamine, these metabolites do not contribute significantly to the therapeutic efficacy of the drug.

At the recommended therapeutic dose, selegiline hydrochloride does not affect the activity of MAO-A, the predominant enzyme in the gut. Selegiline hydrochloride is therefore devoid of the "hypertensive crisis" ("cheese reaction"); neither hypertensive reactions nor the need for any special dietary restrictions were ever encountered during long-term (2-8 years) daily administration of the drug. From a retrospective analysis of patients treated with long-term chronic selegiline hydrochloride treatments, it was concluded that there is a statistically significant increase in the life span (by approximately 15 months) of Parkinsonian patients when selegiline hydrochloride is added to their existing therapeutic regimen. The data suggest that the drug may actually suppress the degeneration of the dopaminergic nigrostriatal system to some extent, thereby altering the course of the disease. This observation finds support from 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.

Pharmacokinetics

Radiotracer studies in animals show that selegiline hydrochloride is rapidly and completely absorbed after oral administration, and is extensively metabolized; in animals, elimination of selegiline hydrochloride and its metabolites is virtually complete within a day. In humans, selegiline hydrochloride is highly bound to plasma protein (94% in vitro), but plasma levels of the unchanged drug are not detectable (<1% of the dose administered) following single or multiple oral doses (steady state) of 5-10 mg selegiline hydrochloride. Being a lipophilic substance, selegiline hydrochloride rapidly crosses the blood-brain barrier. Based upon studies in blood platelets, that contain only MAO-B, MAO-B inhibition in man exhibits non-linear kinetics. This is attributable to

the fact that the inhibitory effect of selegiline hydrochloride on MAO-B is irreversible and dissipates only through enzyme resynthesis.

The major metabolites of selegiline hydrochloride are l-amphetamine, l-methamphetamine and N-desmethylselegiline. The results of single dose and steady state pharmacokinetic studies following the oral administration of 5-10 mg selegiline hydrochloride in healthy fasting volunteers are presented in Tables 1 and 2, respectively. Under these conditions, unchanged selegiline hydrochloride could not be detected in either the serum or urine samples (the limit of detection) of the HPLC method utilized in these studies was 10 ng/ml). N-desmethylselegiline exhibited a short half-life ($t_{1/2}$ of 2.1 hrs.) whereas that for l-amphetamine and l-methamphetamine was 17.7 and 20.5 hrs respectively. These three metabolites accounted for 45% of the dose 48 hours after the administration of the drug. After long-term selegiline hydrochloride treatment, amphetamines may be present in the brain at concentrations equivalent to those found after a dose of 10 to 20 mg of methamphetamine. Since the metabolites are the l-isomers, which are 2 to 3 times less pharmacologically active than the d-isomers, adverse effects such as withdrawal symptoms or drug dependency have not been observed. Parkinson patients receiving selegiline hydrochloride exhibit 24-hr 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 hydrochloride dose appears to be metabolized to amphetamine by conversion from methamphetamine.

Table 1: Serum levels and urinary excretion of l-selegiline and metabolites after single oral dose in human volunteers.

Mean Serum Values				
	Cmax (ng/ml)	Tmax (hrs)	AUC	t1/2 (hrs)
L-selegiline	ND	ND	ND	ND
N-desmethylselegiline	19.0	0.9	NC	2.1
L-amphetamine	28.4	3.7	NC	17.7
L-methylamphetamine	39.9	3.1	NC	20.5

NC = not calculable; ND = not determinable

Mean Urinary Excretion Values			
	Total Amount Excreted (ng)		Mol% of dose Admin. Excreted
	24h	48h	%
L-selegiline			ND
N-desmethylselegiline	ND	ND	1.1
L-amphetamine	88.4	88.6	11.6
L-methylamphetamine	451.4	577.8	32.4
	1306.7	1664.1	45.1

ND = not determinable

Table 2: Serum levels and urinary excretion of l-selegiline and metabolites after multiple doses in human volunteers

Mean Serum Trough Values (ng/ml)							
Day							
	1	2	3	4	5	6	7
L-selegiline	0	-	-	-	-	-	-
N-desmethylselegiline	0	0	0	0.2	0.1	-	0.4
L-amphetamine	0	2.3	3.5	3.6	3.5	2.9	3.9
L-methamphetamine	0	5.6	8.4	7.1	10.4	7.1	7.6

Mean Urinary Excretion (ng)						
Day						
	1	2	3	4	5	6
L-selegiline	-	-	-	-	-	-
N-desmethylselegiline	98.2	77.3	52.4	95.0	63.6	51.9
L-amphetamine	303.0	606.0	604.0	694.0	749.6	672.6
L-methamphetamine	1483.0	1789.8	1892.8	2256.0	2376.7	2329.3

Post-mortem examination of the brains of Parkinson patients treated with selegiline hydrochloride have demonstrated 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 hydrochloride; serotonin oxidation, on the other hand, was inhibited by only 65% maximum which, in turn, did not affect the 5-HlAA concentrations in the brain.

Following the intravenous administration of 10 mg selegiline hydrochloride, a half-life of 0.15 hrs for unchanged selegiline hydrochloride was obtained the half-life of N-desmethylselegiline was approximately the same as that found after oral administration (2.7 vs 2.1 hr.) No unchanged selegiline hydrochloride was found in the serum after 3 hr. The extremely short half-life of selegiline hydrochloride is consistent with the inability to detect unchanged selegiline hydrochloride 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 3, 4 and 5, respectively.

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

Long-term (1 year) toxicity studies in rats showed no drug effects on mortality, gross and microscopic pathology. Decreases were noted on bodyweight gain (dose-related in all but 1 group), food consumption (high dose), total bilirubin (some groups) and urine volume (MD & HD groups). Slight increase in urine pH values were noted, as well as a few high AST results. Equivocal changes were noted in serum sodium, potassium and inorganic phosphorous values.

Long-term (1 year) toxicity studies in dogs showed no drug effects on mortality, gross and microscopic pathology. Decreases were noted on bodyweight gain, RBC, Hb and Hct, MCV (HD groups), sodium. Slight increased in relative liver, thymus, spleen weight SGPT, SAP, cholesterol/ or triglycerides, potassium were noted.

Gross pathology showed dark livers in low, medium and high dose groups. Microscopic pathology showed the number of foci of hemosiderin laden macrophages and/or Kupffer cells was slightly and equivocally increased. Lymphoid atrophy seen in 3 high dose group (including the dog taken off drug). Thymic involution seen in several dogs across all groups including controls; marked

involution seen only in 3 high dose group (including the dog taken off drug). Thymic involution seen in several dogs across all groups including controls; marked involution seen only in 3 high dose groups. Preterminal bone marrow smears showed no drug effects.

Long-term toxicity studies in rats and in dogs showed dose-dependent, amphetamine-like symptoms in both species. Reduction in appetite and other pharmacodynamic actions caused only reversible effects and appeared at such high 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. In view of methodological problems with some of these studies, their results must be interpreted with caution.

Table 3: LD_{50} values from acute toxicity studies with Selegiline hydrochloride, and calculation of the therapeutic ratio**

Species	Route	Sex	LD50 mg/kg	Confidence Limit or minimum lethal dose	Therapeutic range**
Rat	P.O.*	M	422	322-535	3014
	P.O.*	F	302	227-407	2161
	S.C.*	M	146	110-194	1044
	S.C.*	F	112	88-142	802
	I.V.	M	75	67-84	539
	I.V.	F	69	61-78	499
Mouse	P.O.*	M	445	363-545	3181
	P.O.*	F	365	287-463	2609
	S.C.*	M	206	161-262	1471
	S.C.*	F	190	152-237	1357
	I.V.	M	49	42-59	356
	I.V.	F	50	41-62	361
	I.P.	M	190	250	1357
Dog	P.O.	M/F	ca.200	200	1429

* Subsequent observation period 24-168 hours
** With respect to 0.14 mg/kg/day/patient

Table 4: Determination of non-toxic doses of selegiline hydrochloride and of the therapeutic range ** from preclinical toxicity studies with repeated oral administration.

Species	Duration (w/m)*	Dose (mg/kg)	No. animals per group	No. toxic dose	Therapeutic range**
Rat	2W	0-80	20/20	-	-
	4W	0-270	8/8	10	71
Rat	6M	0-30	10/10	30	214
Rat	6M	0-90	10/10	10	71
Dog#	6M	0-30	5/5 plus	3-10 ++	
	8W		2/2		21-71
Dog	6M	0-20	2/2	5	36

W = weeks; M = months; ** With respect to 0.14 mg/kg/day patient
# = with recovery period; ++ = no withdrawal effects

Table 5: Effect-free doses of selegiline hydrochloride from reproduction toxicity studies and calculation of the therapeutic range*

Species	Segment	Dose (mg/kg)	# Animals Group	Effect-free dose	Range
Rat	I** (fertility) teratogen reproduction	0.25 50, 100	20F 10M	100	715
Rat	II (teratogen)	0, 5, 1, 5 3.0	(40)***	(3.0)	(21)
Rat	II (teratogen)	0, 4 12, 36	25	4	30
Rabbit	II	0, 25 50, 100	10	100	715
Rat	III (Peri-post-natal)	0, 4, 16 64	24	4	29

* With respect to 0.14 mg/kg/day/patient
** Modified test design, no treatment from 1st-6th day p.c.
***Limited conception rate

Reproduction and teratology studies conducted in rats and rabbits showed that selegiline hydrochloride, in doses of 100 mg/kg had no effect upon fertility or breeding capacity, and was not associated with any teratogenic effect (safety factor of 715 to 1430). Peri-and post-natal development was affected primarily because of secondary and severe toxic effects on the dams consequent upon the excessive pharmacodynamic action of doses of 16 mg/kg and higher. A no-toxic effect level of 4 mg/kg was established in these studies.

Reproductive studies done on 25 female rats given 0, 4, 12 or 36 mg/kg/day on days 6-15 of gestation showed that in dams, there was transient salivation, reduced body tone and piloerection (HD), transient weight loss (HD) and decreased weight gain (MD & HD) and a decrease in dam food consumption. No drug effects were noted on numbers of CL, implants, resorptions, live young, sex ratio, pre- and post-implantation loss, or litter weight. Mean fetal weight was significantly decreased only at the HD group. In the preliminary uncontrolled study, post implantation loss was high and fetal weight was normal but at the lower limit. There were no drug-related effects based on fetal exam.

Reproductive studies on another 24 female Sprague Dawley rats given 0, 4, 16 or 64 mg/kg/day by gavage from day 16 of gestation through day 21 postpartum showed no effects at LD and MD. At HD piloerection was seen. Vaginal bleeding was seen in a few HD dams; abortion was inferred in 3. After 2 to 7 days of treatment, seventeen dams died. "Feebleness" and coma were noted prior to death in some cases. Autopsy performed on the deceased dams showed 6 with hemorragic foci in GI mucosa and 5 with uterine bleeding; it was stated that loss of blood "might" have been the cause of death. (No drug-related gross changes were said to have occurred among survivors). Decreased gain was seen at MD and HD (final weights approximately 90 and 85% of control, respectively). (A smaller decrease was seen at LD but was not statistically significant). Large decreases were noted at HD throughout treatment period; weekly values generally 1/10-1/5 control during gestation and 1/2 control during lactation. Smaller effects were seen at MD (maximum effect about 2/3 control). No effects were seen at LD. At HD, only 4 pregnant dams survived for assessment. There were no drug effects during gestation. The number of pups/dam at birth slightly decreased in all groups (12.8,

11.5, 11.4, and 10.5 in control, LD, MD, and HD, respectively). The number of stillbirths per dam increased at HD and was equivocal at MD (0.2, 0.2, 0.4, and 4.3 in C, LD, MD, and HD, respectively). Pup survival decreased at MD and HD. The percentage of pups which were alive at day 14 were 95, 97, 53, and 0% in C, LD, MD, HD, respectively. Deaths at MD were spread out over the first 14 days postpartum; at HD all deaths occurred by day 4 postpartum. There were no pup deaths from day 14 to 21 PP). Pup survival decreased at birth at MD and HD (95 and 67% of C, respectively), and through day 21 PP at MD (approximately 90% of control). No living pups were available at HD for post-partum weighing). Pinna unfolding was slightly delayed at MD by about 1/2 day; other developmental milestones and behavioural observations not affected. The HD was not assessed. No drug-related gross malformations were said to have occurred.

Selegiline hydrochloride did not have any mutagenic potential in a number of tests on gene and chromosome mutations in prokaryotic and eukaryotic cells as well as in cell culture and in vivo. Likewise, no effects on DNA or induction of cell transformation processes, which might form the basis of carcinogenic activity, were noted. The extensive human research conducted on selegiline hydrochloride over the past 15 years also has not shown any carcinogenic potential for this drug. Moreover, none of the metabolites of selegiline hydrochloride have been identified as carcinogens. The data to date tends to indicate that selegiline hydrochloride is neither a mutagen nor a carcinogen.

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