The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques

XXVIIth Canadian Congress of Neurological Sciences
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The Official Journal of

The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

Volume 18, No. 3 **August 1991**

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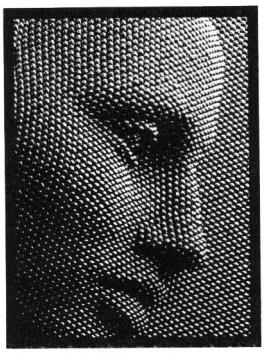

Prescribing Information

ACTION AND CLINICAL PHARMACOLOGY

SIBELIUM* (flunarizine hydrochloride) prevents the deleterious effects of cellular calcium overload by reducing excessive transmembrane fluxes of calcium. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7 – 79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (< 0.2%) and fecal (< 6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Table I: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h)	$t_{1/2\alpha}$ (h)	Clp (mL/min)	$t_{1/2\beta}$ (mean days) [range]
Single Dose Studies		5	30.5	2-4	133[a]	2.4		
		10	81.5		615[a]	2.8		
		20	117.0		1091[a]	3.6		
		30	81.6	2-6	1169[c]	5	443.7	4 [2-8]
Multiple Dose Studies	14	5	18.1[b]					
	14	10	38.8[b]					
	14	15	68.4[b]		1264[d]		301.2	[4-19]
	57	10	114.5		1678[d]			19

a Area under curve 0 to 8 hours
b Plasma concentrations at 2 hours
c Area under curve 0 to 168 hours
d Area under curve 0 to 24 hours

INDICATIONS AND CLINICAL USE

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. Flunarizine is not indicated in the treatment of acute migraine attacks.

CONTRAINDICATIONS

SIBELIUM (flunarizine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

Flunarizine is contraindicated in patients with a history of depression or pre-existing extrapyramidal disorders.

PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with SIBELIUM (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. Breast feeding should therefore be discouraged in women taking flunarizine.

Use in the Elderly

The efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

Use in Children

The efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

Use in Patients with Parkinson's Disease

Flunarizine is contraindicated in patients with pre-existing Parkinson's disease or other extrapyramidal disorders (see CONTRAINDICATIONS). Clinical studies indicate that prolonged flunarizine treatment, even at recommended doses, can produce motor disturbances in elderly subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely so that extrapyramidal symptoms may be detected early and if necessary, treatment discontinued.

Use in Depressive Patients

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression mostly in younger patients (see CONTRAINDICATIONS).

Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

ADVERSE REACTIONS

In clinical trials with SIBELIUM (flunarizine hydrochloride) migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal: Heartburn, nausea, emesis, gastralgia;
Central Nervous System: Insomnia and sleep change, anxiety, dizziness/vertigo;
Miscellaneous: Dry mouth, asthenia, muscle aches, skin rash

SYMPTOMS AND TREATMENT OF OVERDOSE

There has been no experience to date with overdosage of SIBELIUM (flunarizine hydrochloride). Based on the pharmacological properties of the drug, sedation and asthena may be expected to occur. Treatment should consist of induction of emesis or gastric lavage and supportive measures.

DOSAGE AND ADMINISTRATION

The usual adult dosage of SIBELIUM (flunarizine hydrochloride) 10 mg per day administered in the evening. Patients who experience side effects may be maintained on 5 mg HS.

Duration of Therapy

Clinical experience indicates that the onset of effect of flunarizine is gradual and maximum benefits may not be seen before the patient has completed several weeks of continuous treatment. Therapy therefore should not be discontinued for lack of response before an adequate time period has elapsed, e.g. 6-8 weeks.

DOSAGE FORMS

Composition: Each red and grey capsule contains 5 mg flunarizine (as hydrochloride).
Availability: SIBELIUM flunarizine hydrochloride capsules are available in blister packages of 60 capsules.
Storage: SIBELIUM capsules 5 mg should be stored at or below 25°C, protected from light and moisture.

Product monograph available on request

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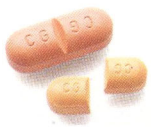

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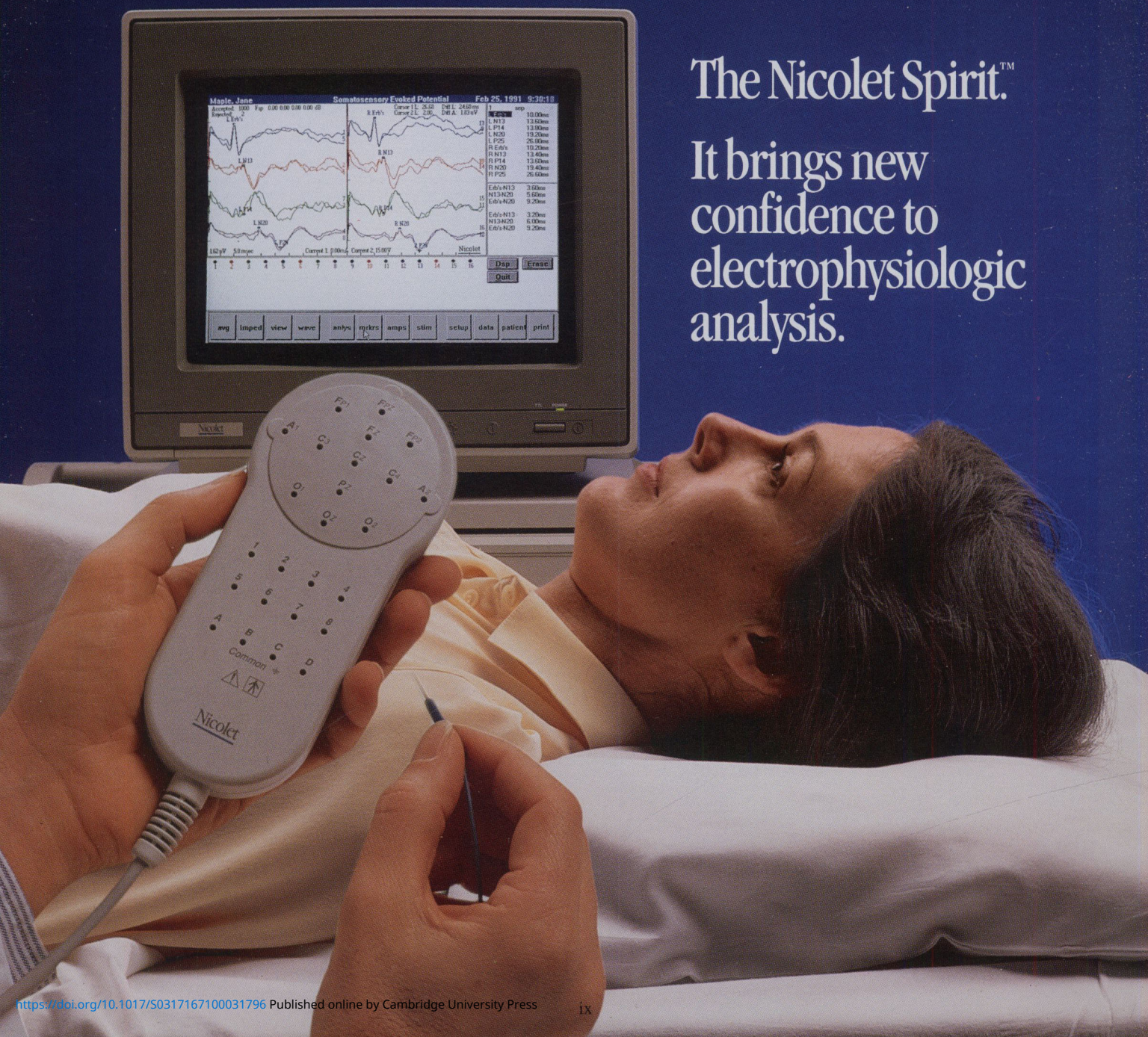

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PELDEPRYL® *Adjunct In The Management Of Parkinson's Disease*

(selegiline hydrochloride) (l-deprenyl hydrochloride) TABLETS 5 mg

ACTIONS AND CLINICAL PHARMACOLOGY ELDEPRYL (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. The mechanism of action of ELDEPRYL 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 ELDEPRYL, 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, ELDEPRYL 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 patients with Parkinsonism because of side effects, such as hypertension, increase in involuntary movements and toxic delirium. Toxic delirium has also been reported with ELDEPRYL 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 ELDEPRYL at a dose of 10 mg a day, because gut MAO-A is not inhibited, can take medications containing pharmacologically active amines and consume tyramime-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 ELDEPRYL treated patients. However, until the pathophysiology of the "hypertensive crisis" is more completely understood, it seems prudent to assume that ELDEPRYL 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 ELDEPRYL's 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.** Only preliminary information about the details of the pharmacokinetics of ELDEPRYL and its metabolites is available. Data obtained in a study of 12 healthy subjects that was intended to study the effects of ELDEPRYL on the pharmacokinetics of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of ELDEPRYL to these subjects, serum levels of intact ELDEPRYL 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-metamphetamine (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 ELDEPRYL 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-metamphetamine, and those for N-desmethylselegiline were below the levels of detection. The rate of MAO-B regeneration following discontinuation of treatment has not been quantified. 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** ELDEPRYL (selegiline hydrochloride) may be of value as an adjunct to levodopa (usually with a decarboxylase inhibitor) in the management of some patients with Parkinson's Disease. ELDEPRYL is not indicated as a first line treatment of Parkinson patients but may be of value as add-on therapy. Short term benefits from the drug are frequently lost in the longer run. **CONTRAINDICATIONS** ELDEPRYL (selegiline hydrochloride) is contraindicated in patients with known hypersensitivity to this drug. ELDEPRYL 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. **WARNINGS Selective versus Non-selective Inhibition of MAO-B.** ELDEPRYL (selegeline 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 PHARMCOLOGY). The selectivity of ELDEPRYL 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 ELDEPRYL 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. **PRECAUTIONS General.** Some patients given ELDEPRYL (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 by approximately 10 to 30%. The decision to prescribe ELDEPRYL 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 ELDEPRYL. Consequently the full spectrum of possible responses to ELDEPRYL may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe the patients closely for atypical responses. **Warning to Patients.** Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL 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 ELDEPRYL should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided. While hypertensive reactions with ELDEPRYL 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 ELDEPRYL. Transient or continuing abnormalities with tendency for elevated values in liver function tests 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.** Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of ELDEPRYL and other drugs have been reported. Because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. **Carcinogenesis** Studies to evaluate the carcinogenic potential of ELDEPRYL have not been completed. **Use during Pregnancy.** Insufficient animal reproduction studies with ELDEPRYL have been done to conclude that ELDEPRYL 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 ELDEPRYL can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ELDEPRYL 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 ELDEPRYL 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 ELDEPRYL in children have not been evaluated. **ADVERSE REACTIONS Introduction.** THE SIDE EFFECTS OF ELDEPRYL (selegiline HCl) ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. THE DRUG MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA. THEREFORE ADJUSTMENT OF DRUG DOSAGES MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH SOME FREQUENCY WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/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. The number of patients investigated in controlled clinical trials is limited, and therefore the kind of information required to provide an estimate of incidence of adverse reactions is not available. In prospective clinical trials, the following adverse effects, in decreasing order of frequency, led to discontinuation of treatment with ELDEPRYL: 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 once as a cause of 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. In controlled clinical trials involving a very limited number of patients (N = 49 receiving ELDEPRYL; 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

	Number of Patients	
ADVERSE EVENT	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

The following is a list of all adverse reactions reported classified by body system: **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, behavior/mood change, dreams/ nightmares, 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, 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. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** No specific information is available about clinically significant overdoses with ELDEPRYL (selegiline HCl). However, experience gained during the development of ELDEPRYL reveals that some individuals exposed to doses of 600 mg/day of ELDEPRYL suffered severe hypotension and psychomotor agitation. Since the selective inhibition of MAO-B by ELDEPRYL 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, isocarboxazide, and phenelzine]. 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 the overdose. Death has been reported following overdosage with non-selective MAO inhibitors. 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, 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. 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 stimulants 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 ELDEPRYL (selegiline HCl) as an adjunct 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. The dose of 10 mg/day results in an almost complete selective inhibition of MAO-B enzyme. The inhibitory action of ELDEPRYL is irreversible, the duration of drug effect depends on enzyme regeneration. Higher doses will result in a loss of selectivity of ELDEPRYL 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 ELDEPRYL 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 ELDEPRYL to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects. **AVAILABILITY** ELDEPRYL (selegiline HCl) 5 mg tablets, available in bottles of 60 tablets. Each almost white, flat tablet, with one face engraved with "JU", contains 5 mg of the l-isomer of selegiline HCl (formerly l-deprenyl HCl). The inactive ingredients are Lactose, Starch, Povidone, Magnesium Stearate, and Talc. Product Monograph available to physicians and pharmacists upon request.

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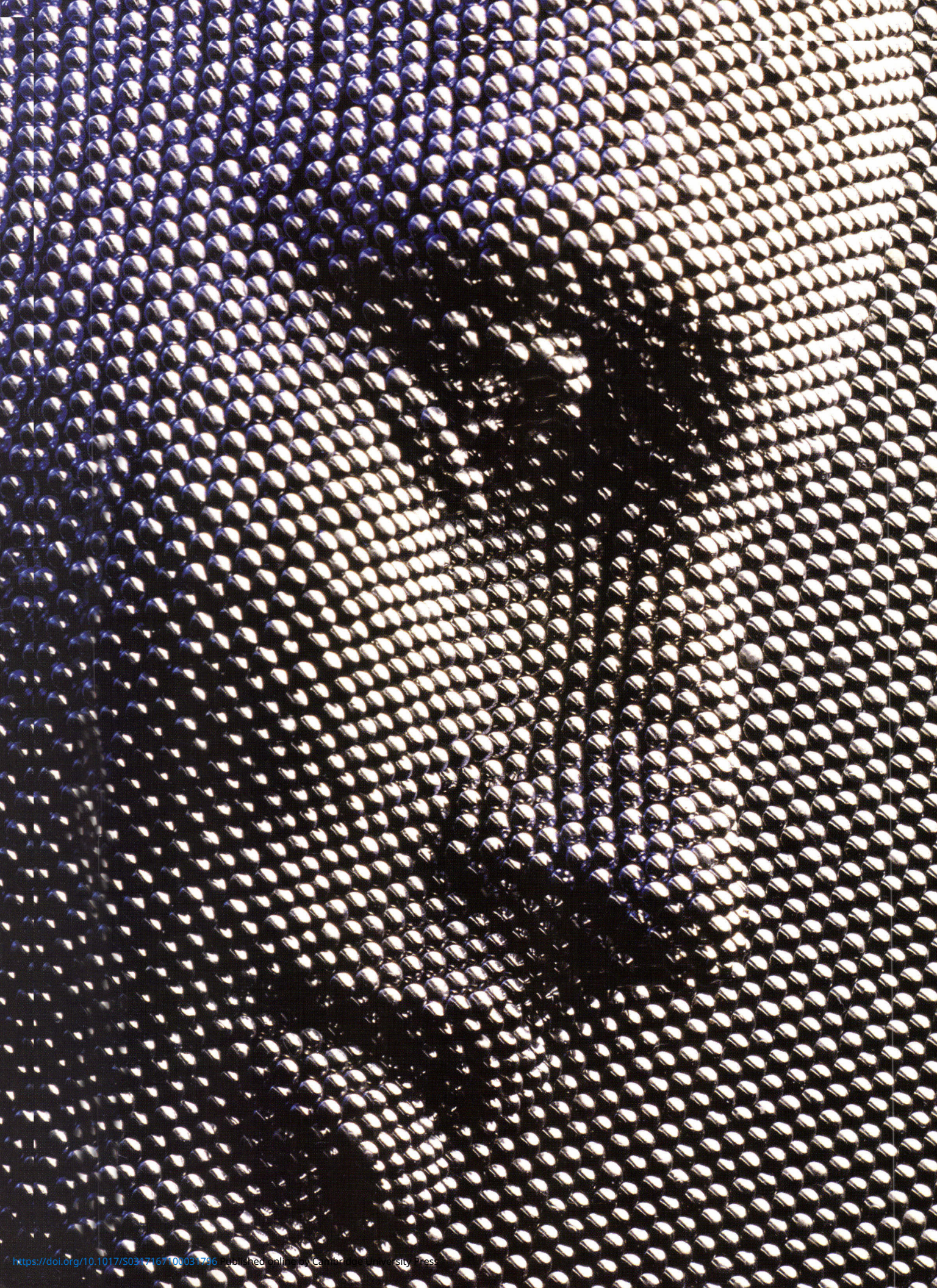

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Prescribing Information

ACTION AND CLINICAL PHARMACOLOGY

SIBELIUM* (flunarizine hydrochloride) prevents the deleterious effects of cellular calcium overload by reducing excessive transmembrane fluxes of calcium. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7 – 79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (< 0.2%) and fecal (< 6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Table I: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h)	t½α (h)	Clp (mL/min)	t½β (mean days) [range]
Single Dose Studies		5	30.5	2-4	133[a]	2.4		
		10	81.5		615[d]	2.8		
		20	117.0		1091[d]	3.6		
		30	81.6	2-6	1169[e]	5	443.7	4 [2-8]
Multiple Dose Studies	14	5	18.1[b]					
	14	10	38.8[b]					
	14	15	68.4[b]		1264[d]		301.2	[4-19]
	57	10	114.5		1678[d]			19

a Area under curve 0 to 8 hours
b Plasma concentrations at 2 hours
c Area under curve 0 to 168 hours
d Area under curve 0 to 24 hours

INDICATIONS AND CLINICAL USE

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. Flunarizine is not indicated in the treatment of acute migraine attacks.

CONTRAINDICATIONS

SIBELIUM (flunarizine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

Flunarizine is contraindicated in patients with a history of depression or pre-existing extrapyramidal disorders.

PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with SIBELIUM (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. Breast feeding should therefore be discouraged in women taking flunarizine.

Use in the Elderly

The efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

Use in Children

The efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

Use in Patients with Parkinson's Disease

Flunarizine is contraindicated in patients with pre-existing Parkinson's disease or other extrapyramidal disorders (see CONTRAINDICATIONS). Clinical studies indicate that prolonged flunarizine treatment, even at recommended doses, can produce motor disturbances in elderly subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely so that extrapyramidal symptoms may be detected early and if necessary, treatment discontinued.

Use in Depressive Patients

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression mostly in younger patients (see CONTRAINDICATIONS).

Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

ADVERSE REACTIONS

In clinical trials with SIBELIUM (flunarizine hydrochloride) migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal:	Heartburn, nausea, emesis, gastralgia;
Central Nervous System:	Insomnia and sleep change, anxiety, dizziness/vertigo;
Miscellaneous:	Dry mouth, asthenia, muscle aches, skin rash

SYMPTOMS AND TREATMENT OF OVERDOSE

There has been no experience to date with overdosage of SIBELIUM (flunarizine hydrochloride). Based on the pharmacological properties of the drug, sedation and asthena may be expected to occur. Treatment should consist of induction of emesis or gastric lavage and supportive measures.

DOSAGE AND ADMINISTRATION

The usual adult dosage of SIBELIUM (flunarizine hydrochloride) 10 mg per day administered in the evening. Patients who experience side effects may be maintained on 5 mg HS.

Duration of Therapy

Clinical experience indicates that the onset of effect of flunarizine is gradual and maximum benefits may not be seen before the patient has completed several weeks of continuous treatment. Therapy therefore should not be discontinued for lack of response before an adequate time period has elapsed, e.g. 6-8 weeks.

DOSAGE FORMS

Composition:	Each red and grey capsule contains 5 mg flunarizine (as hydrochloride).
Availability:	SIBELIUM flunarizine hydrochloride capsules are available in blister packages of 60 capsules.
Storage:	SIBELIUM capsules 5 mg should be stored at or below 25°C, protected from light and moisture.

Product monograph available on request

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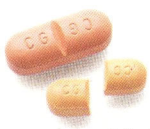

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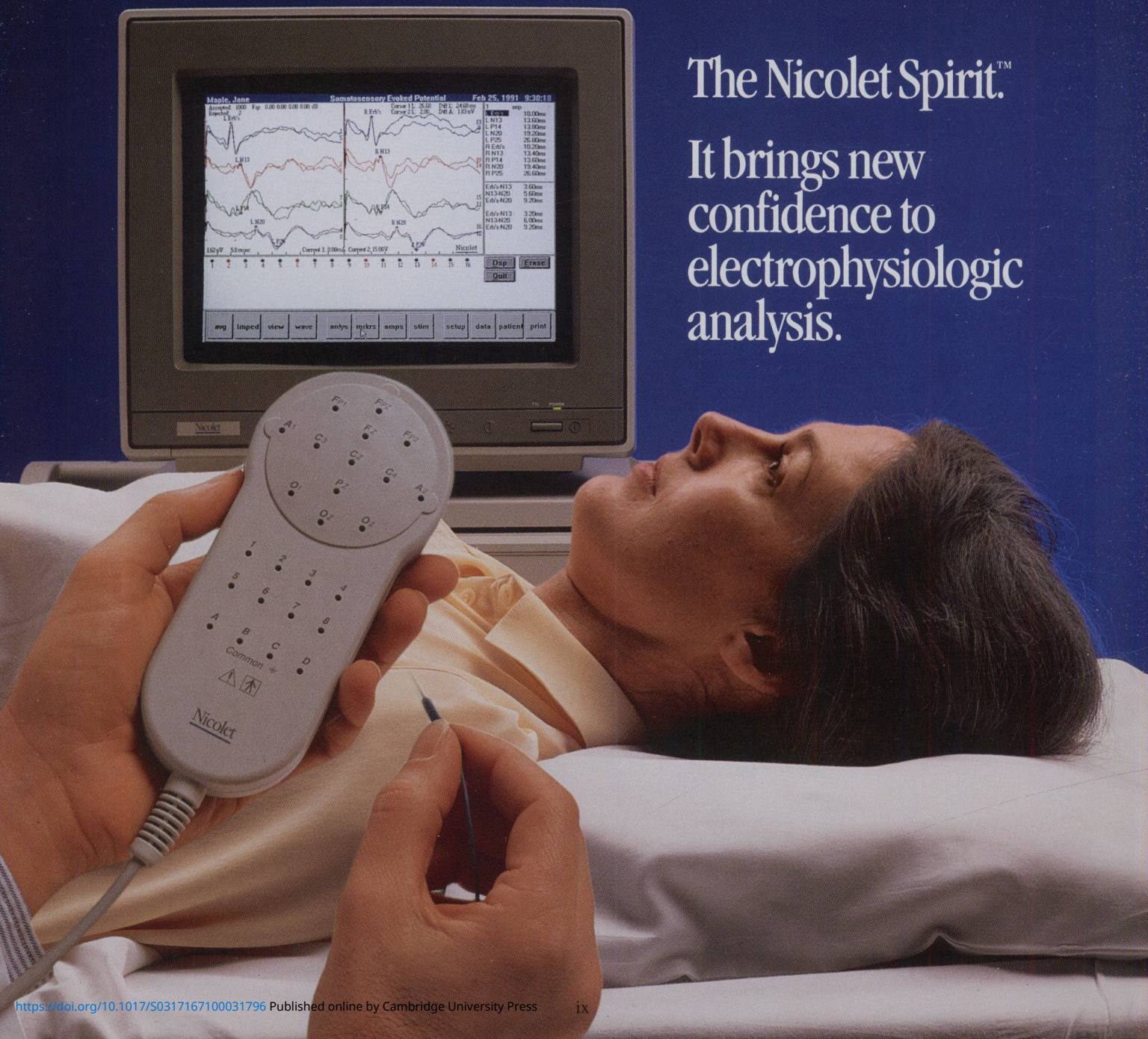

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ELDEPRYL® *Adjunct In The Management Of Parkinson's Disease*

(selegiline hydrochloride) (l-deprenyl hydrochloride) TABLETS 5 mg

ACTIONS AND CLINICAL PHARMACOLOGY ELDEPRYL (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. The mechanism of action of ELDEPRYL 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 ELDEPRYL, 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, ELDEPRYL 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 patients with Parkinsonism because of side effects, such as hypertension, increase in involuntary movements and toxic delirium. Toxic delirium has also been reported with ELDEPRYL 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" (il 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 ELDEPRYL at a dose of 10 mg a day, because gut MAO-A is not inhibited, can take medications containing pharmacologically active amines and consume tyramime-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 ELDEPRYL treated patients. However, until the pathophysiology of the "hypertensive crisis" is more completely understood, it seems prudent to assume that ELDEPRYL 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 ELDEPRYL's 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.** Only preliminary information about the details of the pharmacokinetics of ELDEPRYL and its metabolites is available. Data obtained in a study of 12 healthy subjects that was intended to study the effects of ELDEPRYL on the pharmacokinetics of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of ELDEPRYL to these subjects, serum levels of intact ELDEPRYL 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-metamphetamine (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 ELDEPRYL 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-metamphetamine, and those for N-desmethylselegiline were below the levels of detection. The rate of MAO-B regeneration following discontinuation of treatment has not been quantified. 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** ELDEPRYL (selegiline hydrochloride) may be of value as an adjunct to levodopa (usually with a decarboxylase inhibitor) in the management of some patients with Parkinson's Disease. ELDEPRYL is not indicated as a first line treatment of Parkinson patients but may be of value as add-on therapy. Short term benefits from the drug are frequently lost in the longer run. **CONTRAINDICATIONS** ELDEPRYL (selegiline hydrochloride) is contraindicated in patients with known hypersensitivity to this drug. ELDEPRYL 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. **WARNINGS Selective versus Non-selective Inhibition of MAO-B.** ELDEPRYL (selegeline 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 PHARMCOLOGY). The selectivity of ELDEPRYL 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 ELDEPRYL 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. **PRECAUTIONS General.** Some patients given ELDEPRYL (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 by approximately 10 to 30%. The decision to prescribe ELDEPRYL 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 ELDEPRYL. Consequently the full spectrum of possible responses to ELDEPRYL may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe the patients closely for atypical responses. **Warning to Patients.** Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL 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 ELDEPRYL should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided. While hypertensive reactions with ELDEPRYL 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 ELDEPRYL. Transient or continuing abnormalities with tendency for elevated values in liver function tests 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.** Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of ELDEPRYL and other drugs have been reported. Because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. **Carcinogenesis** Studies to evaluate the carcinogenic potential of ELDEPRYL have not been completed. **Use during Pregnancy.** Insufficient animal reproduction studies with ELDEPRYL have been done to conclude that ELDEPRYL 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 ELDEPRYL can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ELDEPRYL 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 ELDEPRYL 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 ELDEPRYL in children have not been evaluated. **ADVERSE REACTIONS Introduction.** THE SIDE EFFECTS OF ELDEPRYL (selegiline HCl) ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. THE DRUG MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA. THEREFORE ADJUSTMENT OF DRUG DOSAGES MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH SOME FREQUENCY WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/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. The number of patients investigated in controlled clinical trials is limited, and therefore the kind of information required to provide an estimate of incidence of adverse reactions is not available. In prospective clinical trials, the following adverse effects, in decreasing order of frequency, led to discontinuation of treatment with ELDEPRYL: 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 once as a cause of 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. In controlled clinical trials involving a very limited number of patients (N = 49 receiving ELDEPRYL; 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

	Number of Patients	
ADVERSE EVENT	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

The following is a list of all adverse reactions reported classified by body system: **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, behavior/mood change, dreams/ nightmares, 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, 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. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** No specific information is available about clinically significant overdoses with ELDEPRYL (selegiline HCl). However, experience gained during the development of ELDEPRYL reveals that some individuals exposed to doses of 600 mg/day of ELDEPRYL suffered severe hypotension and psychomotor agitation. Since the selective inhibition of MAO-B by ELDEPRYL 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, isocarboxazide, and phenelzine]. 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 the overdose. Death has been reported following overdosage with non-selective MAO inhibitors. 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, 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. 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 stimulants 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 ELDEPRYL (selegiline HCl) as an adjunct 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. The dose of 10 mg/day results in an almost complete selective inhibition of MAO-B enzyme. The inhibitory action of ELDEPRYL is irreversible, the duration of drug effect depends on enzyme regeneration. Higher doses will result in a loss of selectivity of ELDEPRYL 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 ELDEPRYL 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 ELDEPRYL to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects. **AVAILABILITY** ELDEPRYL (selegiline HCl) 5 mg tablets, available in bottles of 60 tablets. Each almost white, flat tablet, with one face engraved with "JU", contains 5 mg of the l-isomer of selegiline HCl (formerly l-deprenyl HCl). The inactive ingredients are Lactose, Starch, Povidone, Magnesium Stearate, and Talc. Product Monograph available to physicians and pharmacists upon request.

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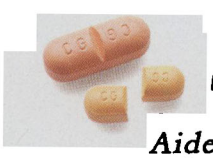

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