



New Zealand Data Sheet

APO-SELEGILINE

Selegiline hydrochloride 5mg Tablets

Presentation

Apo-Selegiline 5mg tablets are white, round, 7.0 mm in diameter, flat faced with bevelled edges and identified "S5" on one side. Each tablet contains 5mg selegiline hydrochloride and typically weighs 155mg.

Uses

Actions

Selegiline is a selective inhibitor of the MAO (monoamine oxidase) enzyme. Since selegiline has a greater affinity for type B than type A MAO it can serve as a selective inhibitor of MAO-B if it is administered at the recommended dose. It also inhibits the re-uptake of dopamine into nerve terminals and blocks presynaptic dopamine receptors which may increase dopaminergic activity in the brain. Two of the principal metabolites of selegiline (amphetamine and methamphetamine) have pharmacological activity of their own and interfere with neuronal re-uptake and enhance the release of several neurotransmitters e.g. norepinephrine, dopamine, serotonin. The extent to which these neurotransmitters contribute to selegiline's effects are unknown.

Studies have shown that patients receiving selegiline as monotherapy for early stage Parkinsonism manage significantly longer without levodopa therapy. After the initiation of levodopa therapy, selegiline potentiates and extend the effect of levodopa allowing a reduction in the levodopa dosage. BY adding selegiline to levodopa therapy the fluctuations in disability e.g. end-of-dose type fluctuations can be reduced.

Unlike non-selective MAO-inhibitors selegiline does not potentiate the hypertensive crises known as "cheese reaction" caused by tyramine like substances. The predominantly intestinal MAO-A is not inhibited by selegiline, so patients treated with selegiline at the dose of 10mg/day can take medication containing pharmacologically active amines and consume tyramine-containing foods without the risk of uncontrolled hypertension.

Pharmacokinetics

Selegiline is rapidly absorbed from the gastrointestinal tract after oral administration with maximal concentrations reached in 0.5 hour. The bioavailability is low with typically only 10% of unchanged selegiline reach the systemic circulation although inter-individual variation is high. Selegiline quickly crosses the blood-brain barrier and is rapidly distributed throughout the body, the apparent volume of elimination being 500 litres after a 10mg intravenous dose. 75-85% of selegiline is bound to plasma proteins at therapeutic concentrations. Selegiline undergoes extensive first pass metabolism in the liver into at least 5 metabolites including N-desmethylselegiline, l-amphetamine and l-methamphetamine with the last two being pharmacologically active.

The mean elimination half-life is 1.6 hours for selegiline and the total body clearance is about 240 L/hour. It is excreted as metabolites mainly in the urine with approximately 15% appearing in the faeces.

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

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No information is available yet concerning polymorphic metabolism or the effect of renal or hepatic insufficiency in the metabolism of selegiline.

Indications

Selegiline is indicated for Parkinson's disease or symptomatic Parkinsonism.

It may be used as a monotherapy in the early stages or combined with levodopa or levodopa plus a peripheral decarboxylase inhibitor. Selegiline combined with levodopa is especially indicated for patients with end-of-dose type fluctuations of disability associated with levodopa therapy on maximum dose levels.

Dosage and Administration

The initial dose is 5mg in the morning. The dose is usually increased to 10 mg per day administered as either 10mg in the morning or two divided doses of 5 mg each taken at breakfast and at lunch.

Doses higher than 10 mg should not be used, as there are no benefits from higher doses. Higher doses will result in a loss of selectivity of Selegiline towards MAO-B with an increase in the inhibition of type MAO-A. Moreover, there is an increased risk of adverse reactions with higher doses as well as the "cheese reaction" with its hypertensive response.

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

Contraindications

- Patients with a known hypersensitivity to selegiline.
- Patients with active peptic ulcers.
- Other extrapyramidal disorders such as excessive tremor or tardive dyskinesia.
- Severe psychosis or profound dementia.

Warnings and Precautions

Selegiline should not be used at daily doses exceeding those recommended (10 mg per day) because of the risks associated with non-selective inhibition of MAO. Doses in the range of 30 to 40 mg per day are known to be non-selective. If higher doses are used there is a risk of hypertension after ingestion of food rich in tyramine.

Fatal interactions of selegiline and meperidine (and other opioids) have led to the warning regarding avoiding their combination.

Some patients given Selegiline may experience an exacerbation of levodopa-associated side effects, due to the increased amounts of dopamine reacting with sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa by approximately 10 to 30%.

Patients should be closely observed for atypical responses since the full spectrum of possible responses to selegiline may not have been observed.

Selegiline should be administered carefully to patients with peptic or duodenal ulcer, labile hypertension, cardiac arrhythmia, severe angina pectoris or psychosis as the drug may exaggerate these conditions.

Use in Pregnancy

Category B2. Safe use in pregnancy has not been established. Therefore, Apo-Selegiline should not be administered during pregnancy unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the foetus.

Use in Nursing Mothers

Selegiline should not be administered to nursing mothers.

Use in Children

The effects of selegiline in children have not been evaluated; therefore selegiline should not be given to children.

Effects on Ability to Drive and Use Machinery

None

Adverse Effects

The reactions which have been most frequently reported with selegiline are associated with excessive dopaminergic stimulation. Selegiline may potentiate the side effects of levodopa therefore some dosage adjustment may be necessary. The most serious adverse reactions reported with selegiline as an adjunct to levodopa therapy are confusion and visual hallucinations.

Extrapyramidal:

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

Psychiatric:

Hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behaviour/mood change, dreams/nightmares, tiredness, delusions, disorientation, light-headedness, impaired memory, increased energy, transient high, hollow feeling, lethargy/malaise, apathy, over-stimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered sensation:

Headache, back and leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalised ache, chills, numbness of toes and fingers and taste disturbances.

Autonomic nervous system:

Dry mouth, blurred vision and sexual dysfunction.

Cardiovascular:

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

Genitourinary:

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

Gastrointestinal:

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

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Dermatological:

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

Other:

Asthma, diplopia, shortness of breath, speech affected.

Laboratory Tests:

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

Interactions

During selegiline therapy the possibility of a hypertensive reaction may occur, as a result of its interaction with indirectly acting sympathomimetic medication. Concomitant use with MAO-A may cause severe hypertension.

Concomitant use of selegiline and moclobemide may result in a significantly increased tyramine sensitivity factor. Dietary restrictions to avoid foods with large amounts of tyramine are recommended when using this combination of medication.

Use with fluoxetine hydrochloride should be avoided as agitation, shivering, hypertension and mania have been reported. Allow at least five weeks between the discontinuation of fluoxetine and the initiation of selegiline. Similar signs have been reported in patients on combination therapy of selegiline and other selective serotonin re-uptake inhibitors including sertraline and paroxetine.

Severe CNS toxicity has been reported in patients taking combinations of selegiline and tricyclic anti-depressants. Reactions include hyperexia, tremors, agitation, restlessness, reduced level of consciousness and in rare instances fatalities. Related adverse events also seen after this combination include hypertension, syncope, asystole, diaphoresis, seizure, change in behaviour and mental status and muscular rigidity.

Selegiline should not be given with meperidine or other opioids due to reports of fatal interactions.

Overdosage

Experience gained during the development of selegiline reveals that some individuals exposed to doses of 600 mg per day suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO-B by selegiline is achieved only at doses recommended for the treatment of Parkinson's Disease (10 mg per day), overdoses are likely to cause significant inhibition of both MAO-A and MAO-B. Consequently the signs and symptoms of overdosage may resemble those observed with non-selective MAO inhibitors. Delays of up to 12 hours between the ingestion of selegiline and the appearance of signs of overdose may occur.

Death has been reported following overdoses with non-selective MAO inhibitors.

Signs and symptoms of overdose may include dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, hypertension, hypotension and vascular collapse, respiratory depression and failure, rapid and irregular pulse, cool clammy skin, diaphoresis, convulsions and coma.

Treatment

There is no specific antidote and the treatment is symptomatic. It is recommended that emesis be induced, and that gastric lavage be performed in early poisoning, provided that the airway has been protected against aspiration. Diazepam given

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slowly intravenously can control the central nervous system stimulation, including convulsions. 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. Adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including airway management, use of supplemented oxygen, and mechanically supported ventilatory assistance, as required. Body temperature should be monitored closely, management of hyperpyrexia may be required and maintenance of fluid and electrolyte balances is essential.

Pharmaceutical Precautions

Store below 30°C. Protect from heat, light and moisture.
Keep container tightly closed.

Medicine Classification

Prescription only medicine

Package Quantities

Bottles of 100 tablets

Further Information

Tablets contain lactose

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