ZELAPAR is taken in the fasted state. Since ZELAPAR is placed on the tongue and absorbed through the pre-gastric absorption from ZELAPAR and the avoidance of first-pass metabolism results in detectable levels of selegiline from ZELAPAR have been measured at 5 minutes after administration, ZELAPAR disintegrates within seconds after placement on the tongue and is rapidly absorbed. It is a suitable option for patients, such as anhedonic or melancholic, social withdrawal, and hypokinetic-rigid subtypes of Parkinson’s disease.

6.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Use ZELAPAR in pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be informed of the potential hazard to a fetus if the drug is used during pregnancy.

6.2 Lactation

It is not known whether selegiline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZELAPAR is administered to nursing women.

6.3 Pediatric Use

Pediatric use is not recommended, since patients with Parkinson’s disease are often elderly and have multiple comorbidities. Their response to treatment is variable and may require frequent dosage adjustments. The duration of treatment also varies among patients and should be determined on an individual basis.

6.4 Hepatic Impairment

In subjects with mild to moderate hepatic impairment (Child-Pugh classes A and B), the pharmacokinetics of selegiline and its metabolites were similar to those in healthy subjects and there is no need to adjust the dose of ZELAPAR. However, patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

6.5 Renal Impairment

In patients with mild to moderate renal impairment (creatinine clearance of 30 to 60 mL/min), the pharmacokinetics of selegiline and its metabolites were similar to those in healthy subjects and there is no need to adjust the dose of ZELAPAR. However, patients with severe renal impairment (creatinine clearance <30 mL/min) have not been studied.

6.6 Supportive and Palliative Care

Supportive respiration, including management of the airway, use of supplemental oxygen, and mechanical ventilation, may be needed in patients with severe selegiline-induced respiratory depression. Supportive respiration is also useful in some patients with selegiline-related myocardial depression or electrocardiographic changes.

6.7 Rheumatic Fever

Rheumatic fever is a serious complication of selegiline overdose. Supportive care, including management of the acute illness, use of supplemental oxygen, and mechanical ventilation, may be needed in patients with severe selegiline-induced respiratory depression. Supportive respiration is also useful in some patients with selegiline-related myocardial depression or electrocardiographic changes.

2.3 Dosage and Administration

The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed under the tongue. The tablet will disintegrate within seconds and be rapidly absorbed. Once it is placed under the tongue, the patient should chew it until it dissolves. If the tablet is swallowed before it is disintegrated, the patient should be advised to try to remove it from the mouth before swallowing. If the tablet is swallowed accidentally, it can be safely managed as a regular oral tablet. Patients should be advised not to become too sedated or drowsy since the drug can cause dizziness or fainting.

2.4 Hyperpyrexia

Hyperpyrexia is a serious, sometimes fatal reaction that may occur in patients treated with selegiline. The syndrome is characterized by high fevers and a variety of neurologic and systemic symptoms, including agitation, delirium, and seizures. It may occur at any time during treatment, and the duration of therapy. If hyperpyrexia occurs, it should be treated with supportive care and temperature management, including use of hypothermia. Supportive care also involves the use of anticonvulsants, including benzodiazepines and barbiturates.

2.5 Hypotension

Hypotension is a common and potentially serious side effect of selegiline treatment. It is characterized by a decrease in blood pressure that may result in dizziness, lightheadedness, and fainting. In patients with pre-existing cardiovascular disease, hypotension may lead to cardiac arrest. Patients should be advised to avoid sudden changes in posture, such as sitting up or standing up from lying down or sitting down from standing up. If hypotension occurs, the patient should be treated with supportive measures, including increasing the dose of selegiline or the dose of a co-administered antihypertensive medication. If hypotension is severe, the patient should be treated with a vasoconstrictor, such as norepinephrine.

8.4 Lactation

It is not known whether selegiline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZELAPAR is administered to nursing women.

8.5 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Use ZELAPAR in pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be informed of the potential hazard to a fetus if the drug is used during pregnancy.

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8.7 Renal Impairment

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13. NONCLINICAL TOXICOLOGY

13.1 Impairment of Fertility

In rats administered selegiline orally (0.3, 1, and 10 mg/kg/day) during gestation and lactation, organogenesis, embryolethality was observed at the highest dose tested and reduced fetal body weight was observed at all dose levels tested. Developmental toxicity was not observed at 0.3 mg/kg/day. In rabbits administered selegiline orally (5, 30, and 60 mg/kg/day) throughout the period of organogenesis, embryolethality was observed at the highest dose tested and reduced fetal body weight was observed at all dose levels tested. In rats administered selegiline orally (1, 5, and 25 mg/kg/day) from postnatal Day 1 to PND 28, reduced body weight gain was observed at the highest dose tested. In rhesus monkeys administered selegiline orally (0.12-1.0 mg/kg/day) from Day 5 to Day 15 of gestation, no toxicity was observed.

13.2 Chromosomal Aberration Assays

Selegiline was negative in the in vitro chromosomal aberration assay in mammalian cells, selegiline was not mutagenic in the in vivo mouse bone marrow micronucleus assay, and selegiline was not genotoxic in the bacterial reverse mutation assay (Ames test) and in vivo mouse bone marrow cytogenetics assay.

13.3 Carcinogenicity Studies

In a 2-year study in Sprague-Dawley rats administered selegiline orally (0.1, 1, and 10 mg/kg/day) and in a 2-year study in B6C3F1 mice administered selegiline orally (0.5, 2, and 10 mg/kg/day), neoplasms of the liver and adrenal gland were increased in a dose-dependent manner. No increases in the incidences of neoplasms were observed in Sprague-Dawley rats administered selegiline orally (1 mg/kg/day) for 1 year and in B6C3F1 mice administered selegiline orally (2 mg/kg/day) for 1 year.

13.4 Toxicity Toward Exogenous Amines

Serious, sometimes fatal reactions have been reported in patients treated with concomitant meperidine and other sympathomimetic amines in overdose. These reactions include severe hypotension, bronchoconstriction, and psychomotor agitation. Uncontrolled hypertension has been reported when taking the recommended dose of swallowed ZELAPAR. If MAO is inhibited in the gastrointestinal tract and liver, ingestion of exogenous amines contained in some foods such as fermented cheese, tomatoes, and olives may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day in patients with concomitant MAOI and other sympathomimetic amines.

7. DRUG INTERACTIONS

7.1 MAO Inhibitors

The concomitant use of selegiline and MAO inhibitors, including isocarboxazid, tranylcypromine, and phenelzine, is strongly discouraged. In patients receiving selegiline in combination with an MAOI, a hypertensive reaction may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day in patients with concomitant MAOI and other sympathomimetic amines.

7.2 CNS-Stimulants

The administration of selegiline could have an additive effect when added to CNS-stimulants such as methylphenidate. If selegiline is added to methylphenidate, dose reductions may be necessary. If methylphenidate is added to selegiline, careful dose titration is recommended.

7.3 Tricyclic Antidepressants

Tricyclic antidepressants, particularly amitriptyline, can cause a rise in blood pressure when used with selegiline. Dose reductions of tricyclic antidepressants may be necessary. If the recommended dose of selegiline is exceeded, discontinuation of one or more of the medications generally used for the treatment of Parkinson’s disease, including MAO inhibitors, or tricyclic antidepressants, may be necessary.

7.4 Antihypertensive Agents

The use of antihypertensive agents and selegiline together may increase the risk of hypotension. Dose reductions of antihypertensive agents may be necessary. If antihypertensive agents are added to selegiline, careful dose titration is recommended.

7.5 Beta-Blockers

The use of beta-blockers and selegiline together may increase the risk of hypotension. Dose reductions of beta-blockers may be necessary. If beta-blockers are added to selegiline, careful dose titration is recommended.

7.6 Antidiabetic Agents

The use of antidiabetic agents and selegiline together may increase the risk of hypoglycemia. If the patient is using insulin or oral antidiabetic agents and is taking selegiline, close monitoring and dose adjustments of these agents may be necessary.

7.7 Anticoagulants

The use of anticoagulants and selegiline together may increase the risk of bleeding. Dose reductions of anticoagulants may be necessary. If anticoagulants are added to selegiline, careful dose titration is recommended.

8.1 Special Populations

No dose adjustment of ZELAPAR is required in patients with mild to moderate renal impairment (creatinine clearance of 30 to 60 mL/min) and patients with end-stage renal disease (CLcr <30 mL/min). The risk of a hypertensive reaction.

8.2 Elderly

Because elderly patients are at greater risk for adverse effects of selegiline, dose reductions may be necessary. Patients should be monitored closely for side effects, and the dose should be increased gradually as tolerated.

8.3 Pediatric Patients

Pediatric use is not recommended, since patients with Parkinson’s disease are often elderly and have multiple comorbidities. Their response to treatment is variable and may require frequent dosage adjustments. The duration of treatment also varies among patients and should be determined on an individual basis.