

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZELAPAR safely and effectively. See full prescribing information for ZELAPAR.

ZELAPAR (selegiline hydrochloride) ORALLY DISINTEGRATING TABLETS

Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Warnings and Precautions

Falling Asleep and Somnolence (5.3)	07/2014
Impulse Control/Compulsive Behaviors (5.7)	07/2014

INDICATIONS AND USAGE

ZELAPAR, a monoamine oxidase type B (MAO-B) inhibitor, is indicated as an adjunct in the management of patients with Parkinson's disease being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy (1)

DOSAGE AND ADMINISTRATION

- Initiate treatment with 1.25 mg given once a day for at least 6 weeks; after 6 weeks, the dose may be escalated to 2.5 mg once a day (2.1)
- Place tablet on top of the tongue where the tablet will disintegrate in seconds; avoid food and liquid intake 5 minutes before and after each dose (2.1)
- In patients with mild or moderate hepatic impairment, the dose should be reduced to 1.25 mg; ZELAPAR is not recommended in patients with severe (Child-Pugh score >9) hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

Orally Disintegrating Tablets: 1.25 mg (3)

CONTRAINDICATIONS

ZELAPAR is contraindicated in patients using the following drugs: meperidine, tramadol, methadone, propoxyphene, MAO inhibitors including selective MAO-B inhibitors, dextromethorphan, St. John's wort, and cyclobenzaprine (4)

WARNINGS AND PRECAUTIONS

- May cause hypertension above 2.5 mg/day (5.1)
- May cause serotonin syndrome when used with antidepressants (5.2)
- May cause falling asleep during activities of daily living (5.3)
- May cause hypotension/orthostatic hypotension (5.4)
- May cause or exacerbate dyskinesia (5.5)
- May cause hallucinations and psychotic-like behavior (5.6)
- May cause problems with impulse control and compulsive behaviors (5.7)
- Abrupt discontinuation may cause hyperpyrexia and confusion (5.8)
- Increased risk of melanoma (5.9)
- May cause irritation of the buccal mucosa (5.10)
- Increased risk for phenylketonuric patients (5.11)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 3% greater than on placebo) are constipation, skin disorders, vomiting, dizziness, dyskinesia, insomnia, dyspnea, myalgia, and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Renal Impairment: ZELAPAR is not recommended in patients with severe renal impairment (CL_{Cr} <30mL/min) (2.3, 8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZELAPAR is indicated as an adjunct in the management of patients with Parkinson's disease being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that ZELAPAR has any beneficial effect in the absence of concurrent levodopa therapy [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage Recommendations

Initiate treatment with 1.25 mg given once a day for at least 6 weeks. After 6 weeks, the dose may be increased to 2.5 mg given once a day if a desired benefit has not been achieved and the patient is tolerating ZELAPAR. There is no evidence that doses greater than 2.5 mg a day provide additional benefit, and they should ordinarily be avoided because of the potential increased risk of adverse events.

Take ZELAPAR in the morning before breakfast and without liquid. Patients should avoid ingesting food or liquids for 5 minutes before and after taking ZELAPAR.

Patients should not attempt to push ZELAPAR through the foil backing. Patients should PEEL BACK the backing of one or two blisters (as prescribed) with dry hands, and GENTLY remove the tablet(s). Patients should IMMEDIATELY place the ZELAPAR tablet(s) on top of the tongue where it will disintegrate in seconds.

2.2 Patients with Hepatic Impairment

In patients with mild to moderate hepatic disease (Child-Pugh score 5 to 9), the daily dose of ZELAPAR should be reduced (from 2.5 to 1.25 mg daily), depending on the clinical response. ZELAPAR is not recommended in patients with severe hepatic impairment (Child-Pugh score greater than 9) [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.3 Patients with Renal Impairment

No dose adjustment of ZELAPAR is required in patients with mild to moderate renal impairment (creatinine clearance [CLCr] 30 to 89 mL/min). The maintenance dose of ZELAPAR (1.25 mg or 2.5 mg) is determined by the individual clinical response. ZELAPAR is not recommended in patients with severe renal impairment and patients with end-stage renal disease [ESRD] (creatinine clearance [CLCr] <30 mL/min) [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

ZELAPAR Orally Disintegrating Tablets contain 1.25 mg selegiline hydrochloride.

4 CONTRAINDICATIONS

ZELAPAR is contraindicated in patients using meperidine, tramadol, methadone, or propoxyphene. Serotonin syndrome, a potentially serious condition, which can result in death, has been reported with concomitant use of meperidine (e.g., Demerol and other trade names). At least 14 days should elapse between discontinuation of ZELAPAR and initiation of treatment with these medications [see *Warnings and Precautions* (5.2)].

ZELAPAR is contraindicated in patients on any other MAO inhibitor (selective or non-selective), because of an increased risk for hypertensive crisis. At least 14 days should elapse between discontinuation of ZELAPAR and initiation of treatment with any MAO inhibitor.

ZELAPAR is contraindicated in patients using St. John's wort, or cyclobenzaprine (a tricyclic muscle relaxant).

ZELAPAR is contraindicated in patients using dextromethorphan, because of reported episodes of psychosis or bizarre behavior.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

ZELAPAR should not be used at daily doses exceeding those recommended (2.5 mg/day) because of the risks associated with non-selective inhibition of MAO [see *Drug Interactions* (7.3) and *Clinical Pharmacology* (12.2)].

The selectivity of ZELAPAR for MAO-B may not be absolute even at the recommended daily dose of 2.5 mg a day. The selectivity of MAO-B inhibitors, typically decreases and it is ultimately lost as the dose is increased beyond recommended doses. Hypertensive reactions associated with ingestion of tyramine containing foods have been reported even in patients taking the recommended daily dose of swallowed selegiline, a dose which is generally believed to be selective for MAO-B. Selectivity for MAO-B inhibition is gradually lost with increasing daily doses. An increase in tyramine sensitivity for blood pressure responses appears to begin at a dose of 5 mg ZELAPAR daily [see *Drug Interactions* (7.5)]. However, the precise dose at which ZELAPAR becomes a non-selective inhibitor of all MAO enzymes in individual patients is unknown.

Reports of hypertensive reactions have occurred in patients who ingested tyramine-containing consumables (i.e., food or drink) while receiving swallowed selegiline at the recommended dose (a dose believed to be relatively selective for MAO-B).

The safe use of ZELAPAR at doses above 2.5 mg daily without dietary tyramine restrictions has not been established.

A pharmacodynamic study showed increased tyramine sensitivity for increasing blood pressure and decreased selectivity for MAO-B with dosing above the recommended level (2.5 mg daily) [see *Clinical Pharmacology* (12.2)].

Uncontrolled hypertension has been reported when taking the recommended dose of swallowed selegiline and a sympathomimetic medication (ephedrine).

After starting ZELAPAR, monitor patients for new onset hypertension or exacerbation of hypertension that is not adequately controlled.

5.2 Serotonin Syndrome

Serotonin syndrome and hyperpyrexia have been reported with the combined treatment of an antidepressant (e.g., selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors-SNRIs, tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants) and a non-selective MAOI (e.g., phenelzine, tranylcypromine) or selective MAO-B inhibitors, such as selegiline (Eldepryl), rasagiline (AZILECT), and Zydys selegiline (ZELAPAR).

Serotonin syndrome is a potentially serious condition, which can result in death. Typical clinical signs and symptoms include behavioral and cognitive/mental status changes (e.g., confusion, hypomania, hallucinations, agitation, delirium, headache, and coma), autonomic effects (e.g., syncope, shivering, sweating, high fever/hyperthermia, hypertension, hypotension, tachycardia, nausea, diarrhea), and somatic effects (e.g., muscular rigidity, myoclonus, muscle twitching, hyperreflexia manifested by clonus, and tremor).

In the post-marketing period, fatal and non-fatal cases of serotonin syndrome have been reported in patients treated with antidepressants concomitantly with ZELAPAR [see *Contraindications (4)* and *Drug Interactions (7.1, 7.2, 7.3)*].

Clinical studies of ZELAPAR did not allow concomitant use of any selective serotonin re-uptake inhibitor (e.g., fluoxetine-Prozac, fluvoxamine-Luvox, paroxetine-Paxil, sertraline, venlafaxine-Effexor, or nefazadone-Serzone) or any non-selective serotonin reuptake inhibiting antidepressant drug (except when taken at a low dose and only at night for the purpose of effective sleep) with ZELAPAR.

Because the mechanisms responsible for these reactions are not fully understood, avoid the combination of ZELAPAR with any antidepressant. At least 14 days should elapse between discontinuation of ZELAPAR and initiation of treatment with a SSRI, SNRI, tricyclic, tetracyclic, or triazolopyridine antidepressant. In patients taking antidepressants with a long half-life (e.g., fluoxetine and its active metabolite), allow at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) to elapse between discontinuation of fluoxetine and initiation of ZELAPAR [see *Drug Interactions (7.6)*].

5.3 Falling Asleep During Activities of Daily Living and Somnolence

Patients with Parkinson's disease treated with ZELAPAR or other drugs increasing dopaminergic tone have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents.

Although many of these patients reported somnolence, some did not perceive warning signs, such as excessive drowsiness, and believed that they were alert immediately prior

to the event. Some of these events have been reported as late as one year after initiation of treatment.

It has been reported that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment.

Somnolence may occur in patients receiving ZELAPAR. There was an increased risk for somnolence in geriatric patients (≥ 65 years) vs non-geriatric patients treated with ZELAPAR. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with ZELAPAR. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with ZELAPAR.

Before initiating treatment with ZELAPAR, advise patients about the potential to develop drowsiness and specifically ask about factors that may increase this risk, such as concomitant sedating medications and the presence of sleep disorders. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), ZELAPAR should ordinarily be discontinued. If a decision is made to continue ZELAPAR, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.4 Hypotension/Orthostatic Hypotension

Assessments of orthostatic (supine and standing) blood pressures at different times throughout the 12 week study period in two controlled trials showed that the frequency of orthostatic hypotension (>20 mm Hg decrease in systolic blood pressure and/or >10 mm Hg decrease in diastolic blood pressure) was greater with ZELAPAR treatment than with placebo treatment. Patients taking ZELAPAR were most likely to experience a decline in systolic and diastolic blood pressure at 8 weeks (2 weeks after initiating 2.5 mg ZELAPAR). At that time, the incidence of systolic orthostatic hypotension was about 21% in ZELAPAR-treated patients and 9% in placebo-treated patients. The incidence of diastolic orthostatic hypotension was about 12% in ZELAPAR-treated patients and about 4% in placebo-treated patients. Thus, it appears that there may be an increased risk for orthostatic hypotension in the period after increasing the daily dose of ZELAPAR[®] from 1.25 to 2.5 mg.

The incidence of orthostatic hypotension was higher in geriatric patients (≥ 65 years) than in non-geriatric patients. In the geriatric patients, orthostatic hypotension occurred in about 3% of ZELAPAR-treated patients compared to 0% of placebo-treated patients.

5.5 Dyskinesia

ZELAPAR may potentiate dopaminergic side effects of levodopa and may cause dyskinesia or exacerbate preexisting dyskinesia. In controlled trials, the incidence of dyskinesia was 6% in ZELAPAR-treated patients and 3% in placebo-treated patients.

Decreasing the dose of levodopa may lessen dyskinesia. The incidence of dyskinesia causing study discontinuation was greater on ZELAPAR than on placebo.

5.6 Hallucinations/Psychotic-Like Behavior

In controlled trials, hallucination was reported by 4% of ZELAPAR-treated patients and 2% in placebo-treated patients. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in about 1% of ZELAPAR-treated patients, compared to no patient on placebo.

Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during ZELAPAR treatment or after starting or increasing the dose of ZELAPAR. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should ordinarily not be treated with ZELAPAR because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of ZELAPAR [see *Drug Interactions (7.10)*].

5.7 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including ZELAPAR, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge eating, or other urges while being treated with ZELAPAR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ZELAPAR.

5.8 Withdrawal Emergent Hyperpyrexia and Confusion

Although not reported with ZELAPAR in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

5.9 Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general

population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using ZELAPAR for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

5.10 Irritation of the Buccal Mucosa

In the controlled clinical trials, periodic examinations of the tongue and oral mucosa were performed. At the end of the study, the frequency of mild oropharyngeal abnormality (e.g., swallowing pain, mouth pain, discrete areas of focal reddening, multiple foci of reddening, edema, and/or ulceration) in patients without similar abnormality at baseline was 10% in ZELAPAR-treated patients compared to 3% in placebo-treated patients.

5.11 Risk for Phenylketonuric Patients

It is important to note that each ZELAPAR tablet contains 1.25 mg phenylalanine (a component of aspartame). Patients taking the 2.5 mg dose of ZELAPAR will receive 2.5 mg phenylalanine.

5.12 Effect on Renal Function

Small increments in serum BUN and creatinine have been observed in patients treated with high dose ZELAPAR (10 mg daily; 4 times the recommended dose).

6. ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling.

- Risk for Hypertension [see *Warnings and Precautions (5.1)*]
- Risk of Serotonin Syndrome [see *Warnings and Precautions (5.2)*]
- Falling Asleep During Activities of Daily Living and Somnolence [see *Warnings and Precautions (5.3)*]
- Hypotension/Orthostatic Hypotension [see *Warnings and Precautions (5.4)*]
- Dyskinesia [see *Warnings and Precautions (5.5)*]
- Hallucinations/Psychotic-Like Behavior [see *Warnings and Precautions (5.6)*]
- Impulse Control / Compulsive Behaviors [see *Warnings and Precautions (5.7)*]
- Withdrawal Emergent Hyperpyrexia and Confusion [see *Warnings and Precautions (5.8)*]
- Melanoma [see *Warnings and Precautions (5.9)*]
- Irritation of the Buccal Mucosa [see *Warnings and Precautions (5.10)*]
- Risk for Phenylketonuric Patients [see *Warnings and Precautions (5.11)*]
- Effect on Renal Function [see *Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions (number of unique patients experiencing an adverse reaction per total

number of patients treated) observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the incidence of adverse reactions observed in clinical practice.

Because the controlled trials performed during premarketing development both used a titration design (1.25 mg per day for 6 weeks, followed by 2.5 mg per day for 6 weeks), with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

The most common adverse reactions (treatment difference incidence at least 3% greater than placebo incidence) reported in the double-blind, placebo-controlled trials during ZELAPAR treatment were constipation, skin disorders, vomiting, dizziness, dyskinesia, insomnia, dyspnea, myalgia, and rash (See Table 1).

Of the 194 patients treated with ZELAPAR in the double-blind, placebo-controlled trials, 5% discontinued due to adverse reactions compared to 1% of the 98 patients who received placebo. Most common adverse reactions causing discontinuation of treatment included dizziness, chest pain, accidental injury, and myasthenia.

Incidence in controlled clinical trials

Table 1 lists the adverse events reported in the placebo-controlled trials after at least one dose of ZELAPAR (incidence 2% or greater).

Table 1: Treatment-Emergent Adverse Events* Incidence in Double-Blind, Placebo-Controlled Trials (Events $\geq 2\%$ of Patients Treated with ZELAPAR and Numerically More Frequent than the Placebo Group)

<u>Body System/ Adverse Event</u>	<u>ZELAPAR[†] 1.25/2.5 mg N=194 %</u>	<u>Placebo[†] N=98 %</u>
Body as a Whole		
Back Pain	5	3
Chest Pain	2	0
Pain	8	7
Cardiovascular System		
Hypertension	3	2
Digestive System		
Constipation	4	0
Diarrhea	2	1
Dysphagia	2	1
Dyspepsia	5	3
Flatulence	2	1
Nausea	11	9
Stomatitis	5	4
Tooth Disorder	2	1
Vomiting	3	0
Hemic and Lymphatic System		
Ecchymosis	2	0
Metabolic and Nutritional Disorders		
Hypokalemia	2	0
Musculoskeletal System		
Leg Cramps	3	1
Myalgia	3	0
Nervous System		
Ataxia	3	1
Depression	2	1
Dizziness	11	8
Dry Mouth	4	2
Dyskinesia	6	3
Hallucinations	4	2
Headache	7	6
Insomnia	7	4
Somnolence	3	2
Tremor	3	1
Respiratory System		
Dyspnea	3	0
Pharyngitis	4	2

Rhinitis	7	6
Skin and Appendages		
Rash	4	1
Skin Disorders**	6	2

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus patients may be included in more than one category.

** Skin disorders represent any new skin abnormality that would not be characterized as rash or neoplastic lesion. These include events such as skin ulcer, fungal dermatitis, skin hypertrophy, contact dermatitis, herpes simplex, dry skin, sweating, urticaria, and pruritus.

† Patients received concomitant levodopa.

Treatment-emergent adverse reactions for certain events were reported at a higher frequency by patients ≥ 65 years of age compared to patients < 65 years [see *Use in Specific Populations (8.5)*].

No consistent differences in the incidences of adverse reactions were observed between male and female patients.

There were insufficient data to assess the impact of race on the incidence of adverse reactions.

7 DRUG INTERACTIONS

7.1 Meperidine

Serious, sometimes fatal reactions have been reported in patients treated with concomitant meperidine (e.g., Demerol and other tradenames) and MAO inhibitors including selective MAO-B inhibitors [see *Contraindications (4)*].

7.2 Dextromethorphan

The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Therefore, in view of ZELAPAR's MAO inhibitory activity, dextromethorphan should not be used concomitantly with ZELAPAR [see *Contraindications (4)*].

7.3 MAO Inhibitors

ZELAPAR should not be administered along with other selegiline products (e.g., EMSAM or ELDEPRYL[®]) because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis [see *Contraindications (4)*].

7.4 Sympathomimetic Medications

Uncontrolled hypertension, including hypertensive crisis, has been reported when taking the recommended dose of swallowed selegiline and a sympathomimetic medication (ephedrine).

7.5 Tyramine/Selegiline Interaction

The enzyme, monoamine oxidase (MAO) (primarily type A), in the gastrointestinal tract and liver provides protection from ingested amines (e.g., tyramine) that, if absorbed, have the capacity to cause uncontrolled hypertension (tyramine reaction). If MAO is inhibited in the gastrointestinal tract and liver, ingestion of exogenous amines contained in some

foods such as fermented cheese, herring, or over-the-counter cough/cold medicines may be absorbed systemically causing release of norepinephrine and a rise in systemic blood pressure with the potential for uncontrolled hypertension. Selective MAO-B inhibitors lose their selectivity for MAO-B when taken in doses higher than recommended. Non-selective MAO-A inhibitors or MAO-B inhibitors in higher than recommended doses may result in MAO-A inhibition in the gastrointestinal tract and liver.

Results of a tyramine challenge study indicate that ZELAPAR is relatively selective for MAO-B at the recommended dose. In most cases, there is no need for dietary tyramine restriction in patients prescribed ZELAPAR [see *Clinical Pharmacology (12.2)*] at the recommended dose. Because the selectivity for inhibiting MAO-B diminishes as the dose of ZELAPAR is increased above the recommended daily dose, patients should not take more than 2.5 mg of ZELAPAR daily.

Reports of hypertensive reactions have occurred in patients who ingested tyramine-containing consumables (i.e., food or drink) while receiving swallowed selegiline at the recommended dose (a dose believed to be relatively selective for MAO-B). Hypertensive crisis has also been reported with ZELAPAR use that was not above the recommended dosing.

Uncontrolled hypertension has been reported when taking the recommended dose of swallowed selegiline and a sympathomimetic medication (ephedrine).

7.6 Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors

Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and swallowed selegiline, or selective serotonin reuptake inhibitors and swallowed selegiline [see *Warnings and Precautions (5.2)*].

7.7 Drugs that Induce CYP450

Adequate studies have not been done investigating the effect of CYP3A4-inducers on selegiline. Drugs that induce CYP3A4 (e.g., phenytoin, carbamazepine, nafcillin, phenobarbital, and rifampin) should be used with caution.

7.8 Dopaminergic Antagonists

It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of ZELAPAR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animal studies, administration of selegiline during pregnancy was associated with developmental toxicity (decreased embryofetal and postnatal offspring growth and survival) at doses greater than those used clinically. ZELAPAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats administered selegiline orally (5, 10, and 40 mg/kg/day) throughout the period of organogenesis, a decrease in fetal body weight was observed at the mid and high doses. The no-effect dose for embryofetal developmental toxicity in rats (5 mg/kg/day) is approximately 20 times the maximum recommended human dose (MRHD) of 2.5 mg/day on a mg/m² basis.

In rabbits administered selegiline orally (5, 30, and 60 mg/kg/day) throughout the period of organogenesis, embryoletality was observed at the highest dose tested and reduced fetal body weight was observed at the mid and high doses. The no-effect dose for embryofetal developmental toxicity in rabbits (5 mg/kg/day) is approximately 40 times the MRHD on a mg/m² basis.

In rats administered selegiline orally (0.3, 1, and 10 mg/kg/day) during gestation and lactation, decreases in offspring survival and body weights were observed at the highest dose tested. The no-effect dose for pre- and postnatal developmental toxicity (1 mg/kg/day) is approximately 4 times the MRHD on a mg/m² basis.

8.3 Nursing Mothers

Selegiline and metabolites were detected in rat milk at levels higher than those in maternal plasma. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZELAPAR is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

The overall incidence of adverse reactions was increased in geriatric patients (≥ 65 years) compared to non-geriatric patients (< 65 years). Clinical studies did not include a sufficient number of geriatric subjects older than 75 years to determine whether they respond differently to ZELAPAR.

Analysis of adverse reaction incidence in each group was conducted to calculate and compare relative risk (ZELAPAR % / Placebo %) for each treatment. The relative risk was ≥ 2 fold higher for ZELAPAR treatment in the geriatric patients compared to the non-geriatric patients for hypertension, orthostatic/postural hypotension [see *Warnings and Precautions (5.4)*]. The incidence of orthostatic hypotension by measurement of blood pressure was also higher in geriatric patients than in non-geriatric patients. In the geriatric patients, the treatment difference for incidence of orthostatic hypotension determined by supine and standing blood measurements was 3%.

8.6 Hepatic Impairment

Patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9) may require a dose reduction of ZELAPAR (from 2.5 to 1.25 mg daily) depending on the clinical response. ZELAPAR is not recommended in patients with severe hepatic impairment (Child-Pugh score > 9) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment of ZELAPAR is required in patients with mild to moderate renal impairment (creatinine clearance [CLCr] 30 to 89 mL/min). ZELAPAR is not recommended in patients with severe renal impairment and patients with end-stage renal disease [ESRD] (CLCr <30 mL/min) [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

10.1 Selegiline

No specific information is available about clinically significant overdoses with swallowed selegiline or ZELAPAR. However, experience gained during development of the 5 mg swallowed dosage form reveals that some individuals exposed to doses of 600 mg of d,l-selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO-B by ZELAPAR is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 2.5 mg/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[®]), isocarboxazid (MARPLAN[®]), and phenelzine (NARDIL[®])]. For this reason, in cases of overdose with selegiline, dietary tyramine restriction should be observed for several weeks to avoid the risk of a hypertensive reaction.

10.2 Overdose with Non-Selective MAO Inhibitors

NOTE: The following description of presenting symptoms and clinical course is based upon overdose descriptions of nonselective MAO inhibitors and does not include information from patients who have overdosed on oral selegiline or ZELAPAR.

Characteristically, signs and symptoms of non-selective MAO inhibitor overdose may not appear immediately. Delays of up to 12 hours between ingestion of 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. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, 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 and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, 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.

10.3 Treatment or Management of Overdose

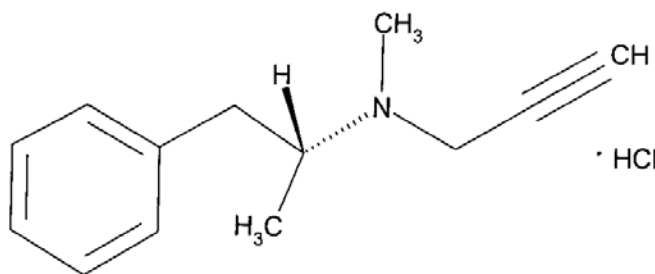
Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system 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.

Support respiration, including management of the airway, use of supplemental oxygen, and mechanical 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.

11 DESCRIPTION

ZELAPAR Orally Disintegrating Tablets contain selegiline hydrochloride, a levorotatory acetylenic derivative of phenethylamine. Selegiline hydrochloride is described chemically as: (-)-(R)-N, α -dimethyl-N-2-propynylphenethylamine hydrochloride and its structural formula is:



Its empirical formula is $C_{13}H_{17}N \cdot HCl$, representing a molecular weight of 223.75. Selegiline hydrochloride is a white to almost white crystalline powder that is freely soluble in water, chloroform, and methanol.

ZELAPAR Orally Disintegrating Tablets are available for oral administration (**not** to be swallowed) in a strength of 1.25 mg. Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, citric acid, yellow iron oxide, and grapefruit flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO), which regulates the metabolic degradation of catecholamines and serotonin in the central nervous system and peripheral tissues. At recommended doses, selegiline is selective for MAO type B (MAO-

B), the major form in the brain. Inhibition of MAO-B activity, by blocking the catabolism of dopamine, may result in increased dopamine levels; however, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

12.2 Pharmacodynamics

A pharmacodynamic study investigating daily ZELAPAR doses of 2.5 mg, 5 mg, and 10 mg for tyramine sensitivity showed that increased tyramine sensitivity resulting in increased blood pressure (because of MAO-A inhibition and decreased selectivity for MAO-B) occurred with dosing above the recommended level (2.5 mg daily). An increase in tyramine sensitivity for blood pressure responses appears to begin at a dose of 5 mg ZELAPAR daily [see *Warnings and Precautions* (5.1)].

12.3 Pharmacokinetics

Absorption

ZELAPAR disintegrates within seconds after placement on the tongue and is rapidly absorbed. Detectable levels of selegiline from ZELAPAR have been measured at 5 minutes after administration, the earliest time point examined.

Selegiline is more rapidly absorbed from the 1.25 or 2.5 mg dose of ZELAPAR (T_{\max} range: 10-15 minutes) than from the swallowed 5 mg selegiline tablet (T_{\max} range: 40-90 minutes). Mean (SD) maximum plasma concentrations of 3.34 (1.68) and 4.47 (2.56) ng/mL are reached after single dose of 1.25 and 2.5 mg ZELAPAR compared to 1.12 ng/mL (1.48) for the swallowed 5 mg selegiline tablets (given as 5 mg bid). On a dose-normalized basis, the relative bioavailability of selegiline from ZELAPAR is greater than from the swallowed formulation.

The pre-gastric absorption from ZELAPAR and the avoidance of first-pass metabolism results in higher concentrations of selegiline and lower concentrations of the metabolites compared to the 5 mg swallowed selegiline tablet.

Plasma C_{\max} and AUC of ZELAPAR were dose proportional at doses between 2.5 and 10 mg daily.

Food effects

When ZELAPAR is taken with food, the C_{\max} and AUC of selegiline are about 60% of those seen when ZELAPAR is taken in the fasted state. Since ZELAPAR is placed on the tongue and absorbed through the oral mucosa, the intake of food and liquid should be avoided 5 minutes before and after ZELAPAR administration [see *Dosage and Administration* (2.1)].

Distribution

Up to 85% of plasma selegiline is reversibly bound to proteins.

Metabolism

Following a single dose, the median elimination half-life of selegiline was 1.3 hours at the 1.25 mg dose. Under steady-state conditions, the median elimination half-life

increases to 10 hours. Upon repeat dosing, accumulation in the plasma concentration of selegiline is observed both with ZELAPAR and the swallowed 5 mg tablet. Steady state is achieved after 8 days.

Selegiline is metabolized *in vivo* to *l*-methamphetamine and *N*-desmethylselegiline and subsequently to *l*-amphetamine; which in turn are further metabolized to their hydroxymetabolites.

ZELAPAR also produces a smaller fraction of the administered dose recoverable as the metabolites than the conventional, swallowed formulation of selegiline.

In vitro metabolism studies indicate that CYP2B6 and CYP3A4 are involved in the metabolism of selegiline. CYP2A6 may play a minor role in the metabolism.

Elimination

Following metabolism in the liver, selegiline is excreted primarily in the urine as metabolites (mainly as *l*-methamphetamine) and as a small amount in the feces.

Special Populations

Age: The effect of age on the pharmacokinetics of selegiline following ZELAPAR administration has not been adequately characterized.

Gender: There are no differences between male and female subjects in overall (AUC_{∞}), time to maximum exposure (T_{max}), and elimination half-life ($t_{1/2}$) after administration of ZELAPAR. Female subjects have an approximate 25% decrease in C_{max} compared to male subjects. However, since the overall exposure (AUC_{∞}) is not different between the genders, this pharmacokinetic difference is not likely to be clinically relevant.

Race: No studies have been conducted to evaluate the effects of race on the pharmacokinetics of ZELAPAR.

Renal Impairment: Following once-daily dosing of ZELAPAR 2.5 mg to selegiline steady-state (10 days) in 6 subjects with mild renal impairment ($CL_{cr} >50$ to 89 mL/min) and in 6 subjects with moderate renal impairment ($CL_{cr} >30$ to 50 mL/min), AUC and C_{max} of selegiline and desmethylselegiline were not substantially different from healthy subjects; however, methamphetamine and amphetamine exposures were increased by 34-67% in subjects with moderate renal impairment. Following once-daily dosing of ZELAPAR 1.25 mg to steady-state (10 days) in 6 end-stage renal disease patients, off dialysis, selegiline exposure was not substantially different from that in healthy subjects, however methamphetamine and amphetamine exposures were increased approximately 4-fold compared to healthy subjects [see *Dosage and Administration* (2.3) and *Use in Specific Populations* (8.7)].

Hepatic Impairment: Subjects with mild hepatic impairment (Child-Pugh score 5 to 6), received once-daily dosing of ZELAPAR 2.5 mg to selegiline until they attained steady-state (10 days). The AUC and C_{max} of selegiline were 1.5-fold higher and the AUC and C_{max} of the metabolite desmethylselegiline were 1.4-fold and 1.2-fold higher. In subjects with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC of selegiline and

desmethylselegiline increased 1.5-fold and 1.8-fold, respectively, whereas the C_{max} of selegiline and demethylselegiline were comparable to healthy subjects. Patients with severe hepatic impairment (Child-Pugh score >9) had a 4-fold increased AUC of selegiline, 3-fold increased C_{max} of selegiline, a 1.25-fold increased AUC of desmethylselegiline and 50% reduced C_{max} of desmethylselegiline. Methamphetamine and amphetamine metabolite AUC values were not affected by liver dysfunction [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.6)].

Drug Interactions: No studies have been conducted to evaluate drug interactions on the pharmacokinetics of ZELAPAR.

Effect of CYP3A inhibitor itraconazole: Itraconazole (200 mg QD) did not affect the pharmacokinetics of selegiline (single 10 mg oral, swallowed dose).

Although adequate studies to investigate the effect of CYP3A4-inducers on selegiline have not been performed, drugs that induce CYP3A4 (e.g., phenytoin, carbamazepine, nafcillin, phenobarbital, and rifampin) should be used with caution.

Drug Interaction Studies

No drug interaction studies have been conducted to evaluate the effects of other drugs on the pharmacokinetics of ZELAPAR or the effect of selegiline on other drugs. *In vitro* studies have demonstrated that selegiline is not an inhibitor of CYP450 enzymes. Selegiline and two of its metabolites, methamphetamine and desmethylselegiline, have little or no potential to induce CYP1A2 and CYP3A4/5 under clinical conditions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Assessment of the carcinogenic potential of selegiline administered orally to mice and rats is ongoing.

Carcinogenicity studies of selegiline have not been conducted using the buccal route.

Mutagenesis

Selegiline was negative in the *in vitro* bacterial reverse mutation (Ames) assay in and the *in vivo* micronucleus assay. In the *in vitro* chromosomal aberration assay in mammalian cells, selegiline was negative in the absence of metabolic activation but was clastogenic in the presence of metabolic activation.

Impairment of Fertility

When selegiline was administered orally to male (5, 10, and 40 mg/kg/day) and female (1, 5, and 25 mg/kg/day) rats prior to and during mating and continuing in females to gestation day 7, a decreased number of implantations was observed at the highest doses tested. In males, a reduction in sperm count and density was observed at the highest dose

tested. The no-effect doses for reproductive impairment in rats (10 mg/kg/day in males and 5 mg/kg/day in females) are approximately 40 (males) and 20 (females) times the maximum recommended human dose of 2.5 mg/day on a mg/m² basis.

No fertility studies have been conducted with selegiline using the buccal route.

14 CLINICAL STUDIES

The effectiveness of ZELAPAR as an adjunct to levodopa/carbidopa in the treatment of Parkinson's disease was established in a multicenter, randomized, placebo-controlled trial (n=140; 94 received ZELAPAR, 46 received placebo) of three months' duration. Patients randomized to ZELAPAR received a daily dose of 1.25 mg for the first 6 weeks, and a daily dose of 2.5 mg for the last 6 weeks. All patients were treated with concomitant levodopa products and could additionally have been on concomitant dopamine agonists, anticholinergics, amantadine, or any combination of these during the trial. COMT (catechol-O-methyl-transferase) inhibitors were not allowed.

Patients with idiopathic Parkinson's disease receiving levodopa were enrolled if they demonstrated an average of at least 3 hours of "OFF" time per day on weekly diaries collected during a 2-week screening period. The patients enrolled had a mean duration of Parkinson's disease of 7 years, with a range from 0.3 years to 22 years.

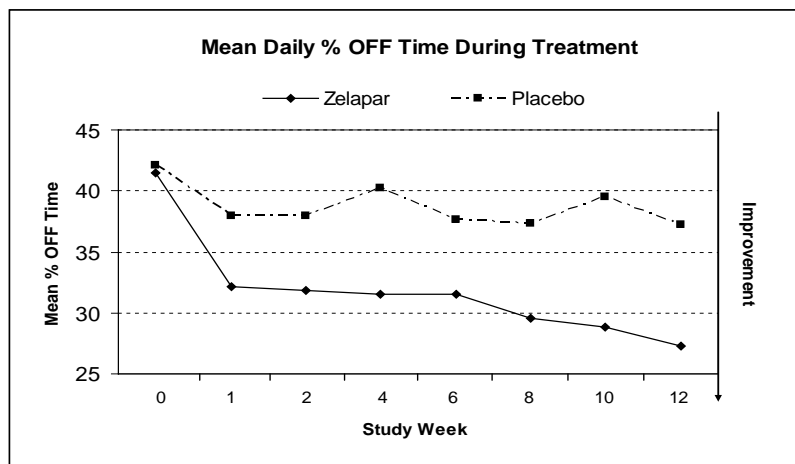
At selected times during the 12-week study, patients were asked to record the amount of "OFF," "ON," "ON with dyskinesia," or "sleep" time per day for two separate days during the week prior to each scheduled visit. The primary efficacy outcome was the reduction in average percentage daily "OFF" time during waking hours from baseline to the end of the trial (averaging results at Weeks 10 and 12). Both treatment groups had an average of 7 hours per day of "OFF" time at baseline. Table 2 shows the primary efficacy results. Patients treated with ZELAPAR had a 13% reduction from baseline in daily "OFF" time, compared with a 5% reduction for patients treated with placebo. ZELAPAR-treated patients had an average reduction from baseline of "OFF" time of 2.2 hours per day, compared with a reduction of 0.6 hours in placebo-treated patients.

Table 2: Mean Percentage Change from Baseline in Daily "Off" Hours at End of Treatment (Average of Weeks 10 and 12) for Intent-to-Treat Population

Treatment	Change from Baseline
Placebo	- 5%
ZELAPAR	- 13%

Figure 1 shows the mean daily percent "OFF" time during treatment over the whole study period for patients treated with ZELAPAR vs. patients treated with placebo.

Figure 1: Mean daily percent “OFF” time during treatment over the whole study period for patients treated with ZELAPAR vs. patients treated with placebo



Dosage reduction of levodopa was allowed during this study if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In those patients who had levodopa dosage reduced, the dose was reduced on average by 24% in ZELAPAR-treated patients and by 21% in placebo-treated patients.

No difference in effectiveness based on age (patients >66 years old vs. <66 years) was detected. The treatment effect size in males was twice that in females, but, given the size of this single trial, this finding is of doubtful significance.

16 HOW SUPPLIED/ STORAGE AND HANDLING

ZELAPAR Orally Disintegrating Tablets are available containing 1.25 mg selegiline hydrochloride in a Zydis[®] formulation. Each pale yellow tablet is imprinted with a stylized “V”. Ten tablets are contained in a moisture-resistant pouch and packaged in a carton. Neither the blister card nor the pouch is child-resistant.

ZELAPAR (selegiline hydrochloride) is available as: NDC 0187-0453-02, carton of 6 pouches (60 tablets).

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Use within 3 months of opening pouch and immediately upon opening individual blister. Store blister tablets in pouch. Potency cannot be guaranteed after 3 months of opening the pouch.

17 PATIENT COUNSELING INFORMATION

Hypertension and Non-Selective Inhibition of MAO Above the Recommended Dose

Advise patients (or their caregivers) not to exceed the daily recommended dose of 2.5 mg. Explain the risk of using higher daily doses of ZELAPAR and provide a brief description of the hypertensive tyramine reaction provided. Rare hypertensive reactions

with oral selegiline at recommended doses associated with dietary influences have been reported.

Inform patients (or their caregivers) about the potential for MAOI-induced hypertensive reactions and describe their signs and symptoms. Instruct patients to report, immediately, severe headache or other atypical or unusual symptoms not previously experienced or very high blood pressure.

The possibility exists that very tyramine-rich foods (e.g., aged cheese such as Stilton) could possibly cause an increase in blood pressure. Patients should be advised to avoid certain foods (e.g., aged cheese) containing a very large amount of tyramine while taking recommended doses of ZELAPAR because of the potential for large increases in blood pressure. If patients eat foods very rich in tyramine and do not feel well soon after eating, they should contact their healthcare provider [see *Warnings and Precautions (5.1)*].

Serotonin Syndrome

Inform patients if they are taking, or planning to take, any prescription or over-the-counter drugs, especially antidepressants and over-the-counter cold medications, because there is a potential for interaction with ZELAPAR. Because patients should not use meperidine or certain other analgesics with ZELAPAR, they should contact their healthcare provider before taking analgesics [see *Warnings and Precautions (5.2)*].

Falling Asleep During Activities of Daily Living and Somnolence

Advise patients about the potential for sedating effects associated with ZELAPAR, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Because somnolence can be a frequent adverse reaction with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with ZELAPAR to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if they experience increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Advise patients not to drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of ZELAPAR [see *Warnings and Precautions (5.3)*].

Hypotension/Orthostatic Hypotension

Advise patients that they may develop symptomatic (or asymptomatic) hypotension while taking ZELAPAR, especially if they are elderly. Hypotension may occur more frequently during initial therapy. Accordingly, caution patients against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with ZELAPAR [see *Warnings and Precautions (5.4)*].

Dyskinesia

Inform patients that ZELAPAR may cause and/or exacerbate pre-existing dyskinesias [see *Warnings and Precautions* (5.5)].

Hallucinations/Psychotic-Like Behavior

Inform patients that hallucinations and other psychotic-like behavior can occur while taking Neupro and that the elderly are at a higher risk than younger patients with Parkinson's disease. Tell patients to report hallucinations or psychotic-like behavior to their health care provider promptly should they develop [see *Warnings and Precautions* (5.6)].

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking one or more of the medications generally used for the treatment of Parkinson's disease, including ZELAPAR. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with ZELAPAR. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking ZELAPAR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking ZELAPAR [see *Warnings and Precautions* (5.7)].

Withdrawal Emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider if they wish to discontinue ZELAPAR or decrease the dose of ZELAPAR [see *Warnings and Precautions* (5.8)].

Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to have periodic examinations of their skin by a qualified healthcare professional on a regular basis when using ZELAPAR [see *Warnings and Precautions* (5.9)].

Irritation of the Buccal Mucosa

Inform patients that ZELAPAR may cause irritation of the buccal mucosa including swallowing pain, mouth pain, discrete areas of focal reddening, edema, and/or ulceration [see *Warnings and Precautions* (5.10)].

Risk for Phenylketonuric Patients

Advise patients that ZELAPAR contains aspartame which could cause problems in patients with phenylketonuria [see *Warnings and Precautions* (5.11)].

Instructions for Use

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where the tablet will disintegrate. Patients

should also avoid drinking liquids or eating food 5 minutes before and after taking ZELAPAR. Use ZELAPAR within 3 months of opening pouch and immediately upon opening individual blister. Store blister tablets in pouch. Potency cannot be guaranteed after 3 months of opening the pouch.

Distributed by:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Catalent Health, Inc.
Swindon, Wiltshire, SN5 8RU, UK

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