

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NOURIANZ® (istradefylline) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

NOURIANZ is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson’s disease (PD) experiencing “off” episodes (1).

DOSAGE AND ADMINISTRATION

- The recommended dosage is 20 mg orally once daily. The dosage may be increased to a maximum of 40 mg once daily (2.1).
- May be taken with or without food (2.1).
- Patients with hepatic impairment: Maximum recommended dosage with moderate hepatic impairment is 20 mg once daily; use of NOURIANZ in patients with severe hepatic impairment should be avoided (2.4, 8.7).
- Patients who smoke 20 or more cigarettes per day (or the equivalent of another tobacco product): Recommended dosage is 40 mg once daily (2.5, 8.8).

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg and 40 mg (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Dyskinesia: Monitor patients for dyskinesia or exacerbation of existing dyskinesia (5.1).
- Hallucinations / Psychotic Behavior: Consider dosage reduction or stopping NOURIANZ if occurs (5.2).
- Impulse Control / Compulsive Behaviors: Consider dosage reduction or stopping NOURIANZ if occurs (5.3).

ADVERSE REACTIONS

The most common adverse reactions (at least 5% and more frequent than placebo) were dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP 3A4 inhibitors: Recommended maximum dosage with concomitant use is 20 mg once daily (2.2, 7.1).
- Strong CYP 3A4 inducers: Avoid use (2.3, 7.1).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

2.2 Dosage Adjustment with Strong CYP 3A4 Inhibitors

2.3 Dosing with Strong CYP 3A4 Inducers

2.4 Dosage Adjustment in Patients with Hepatic Impairment

2.5 Dosage Adjustment for Tobacco Smokers

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Dyskinesia

5.2 Hallucinations / Psychotic Behavior

5.3 Impulse Control / Compulsive Behaviors

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NOURIANZ

7.2 Effect of NOURIANZ on Other Drugs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

8.8 Tobacco Smokers

10 OVERDOSAGE

10.1 Human Experience

10.2 Management of Overdose

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NOURIANZ is indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dosage of NOURIANZ is 20 mg administered orally once daily. The dosage may be increased to a maximum of 40 mg once daily, based on individual need and tolerability. Initial dose titration is not required.

NOURIANZ can be taken with or without food [*see Clinical Pharmacology (12.3)*].

2.2 Dosage Adjustment with Strong CYP 3A4 Inhibitors

The maximum recommended dosage of NOURIANZ with concomitant use of strong CYP3A4 inhibitors is 20 mg once daily [*see Drug Interactions (7.1)*].

2.3 Dosing with Strong CYP 3A4 Inducers

Avoid use of NOURIANZ with strong CYP3A4 inducers [*see Drug Interactions (7.1)*].

2.4 Dosage Adjustment in Patients with Hepatic Impairment

The maximum recommended dosage of NOURIANZ in patients with moderate hepatic impairment (Child-Pugh B) is 20 mg once daily. Closely monitor patients with moderate hepatic impairment for adverse reactions when on NOURIANZ treatment [*see Adverse Reactions (6.1)*]. Avoid use of NOURIANZ in patients with severe hepatic impairment (Child-Pugh C) [*see Use in Specific Populations (8.7)*].

2.5 Dosage Adjustment for Tobacco Smokers

The recommended dosage of NOURIANZ in patients who use tobacco in amounts of 20 or more cigarettes per day (or the equivalent of another tobacco product) is 40 mg once daily [*see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 20 mg tablets: Peach-colored, pillow-shaped, film-coated tablets with "20" debossed on one side.
- 40 mg tablets: Peach-colored, almond-shaped, film-coated tablets with "40" debossed on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Dyskinesia

NOURIANZ in combination with levodopa may cause dyskinesia or exacerbate pre-existing dyskinesia.

In controlled clinical trials (Studies 1, 2, 3, and 4) [see *Clinical Studies (14)*], the incidence of dyskinesia was 15% for NOURIANZ 20 mg, 17% for NOURIANZ 40 mg, and 8% for placebo, in combination with levodopa. One percent of patients treated with either NOURIANZ 20 mg or 40 mg discontinued treatment because of dyskinesia, compared to 0% for placebo.

5.2 Hallucinations / Psychotic Behavior

Because of the potential risk of exacerbating psychosis, patients with a major psychotic disorder should not be treated with NOURIANZ. Consider dosage reduction or discontinuation if a patient develops hallucinations or psychotic behaviors while taking NOURIANZ.

In controlled clinical trials (Studies 1, 2, 3, and 4) [see *Clinical Studies (14)*], the incidence of hallucinations was 2% for NOURIANZ 20 mg, 6% for NOURIANZ 40 mg, and 3% for placebo. In patients treated with NOURIANZ 40 mg, 1% discontinued because of hallucinations, compared to 0% for placebo and 0% for patients treated with NOURIANZ 20 mg. The incidence of “abnormal thinking and behavior” (paranoid ideation, delusions, confusion, mania, disorientation, aggressive behavior, agitation, or delirium) reported as an adverse reaction was 1% for NOURIANZ 20 mg, 2% for NOURIANZ 40 mg, and 1% for placebo.

5.3 Impulse Control / Compulsive Behaviors

Patients treated with NOURIANZ and one or more medication(s) for the treatment of Parkinson’s disease (including levodopa) may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges. In controlled clinical trials (Studies 1, 2, 3 and 4) [see *Clinical Studies (14)*], one patient treated with NOURIANZ 40 mg was reported to have impulse control disorder, compared to no patient on placebo or NOURIANZ 20 mg.

In some postmarketing cases, 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 or compulsive eating, or other urges while being treated with NOURIANZ. Consider dose reduction or discontinuation if a patient develops such urges while taking NOURIANZ [see *Adverse Reactions (6.2)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Dyskinesia [see *Warnings and Precautions (5.1)*]

- Hallucinations / Psychotic Behavior [*see Warnings and Precautions (5.2)*]
- Impulse Control / Compulsive Behaviors [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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 rates observed in practice.

The safety of NOURIANZ was evaluated in 734 patients with Parkinson's disease (PD) taking a stable dose of levodopa and a DOPA decarboxylase inhibitor, with or without other PD medications, in four randomized, multicenter, double-blind, placebo-controlled trials 12 weeks in duration (Studies 1, 2, 3 and 4) [*see Clinical Studies (14)*]. Of the patient population exposed to NOURIANZ, 50% were male, 32% White, 67% Asian, and the mean age was 65 years (range: 33 to 84 years). Of these patients, 356 received NOURIANZ 20 mg and 378 received NOURIANZ 40 mg.

Adverse Reactions Leading to Discontinuation of Treatment

The incidence of patients discontinuing for any adverse reaction was 5% for NOURIANZ 20 mg, 6% for NOURIANZ 40 mg, and 5% for placebo. The most frequently reported adverse reaction causing study discontinuation was dyskinesia [*see Warnings and Precautions (5.1)*].

Common Adverse Reactions in Pooled Placebo-Controlled Trials

Table 1 shows adverse reactions with a frequency of at least 2% in patients treated with NOURIANZ 20 mg or 40 mg once daily. The most common adverse reactions in which the frequency for NOURIANZ was at least 5%, and greater than the incidence on placebo, were dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia.

Table 1: Adverse Reactions with an Incidence of at Least 2% in Patients Treated with NOURIANZ, and Greater than on Placebo, in Pooled Studies 1, 2, 3, and 4

Adverse Reactions	NOURIANZ 20 mg/day (N=356) %	NOURIANZ 40 mg/day (N=378) %	Placebo N=426 (%)
Nervous system disorders			
Dyskinesia	15	17	8
Dizziness	3	6	4
Gastrointestinal disorders			
Constipation	5	6	3
Nausea	4	6	5
Diarrhea	1	2	1
Psychiatric disorders			
Hallucination ¹	2	6	3
Insomnia	1	6	4
Metabolism and nutrition disorders			
Decreased appetite	1	3	1
Investigations			
Blood alkaline phosphatase increased	1	2	1
Blood glucose increased	1	2	0
Blood urea increased	1	2	0
Respiratory, thoracic and mediastinal disorders			
Upper Respiratory Tract Inflammation	1	2	0
Skin and subcutaneous tissue disorders			
Rash	1	2	1

¹ Includes hallucinations, hallucinations visual, hallucinations olfactory, hallucinations somatic, hallucinations auditory.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of istradefylline outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: increased libido.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NOURIANZ

Strong CYP3A4 Inhibitors

Coadministration of NOURIANZ with a strong CYP3A4 inhibitor (ketoconazole) increased istradefylline AUC_{inf} by 2.5-fold [see *Clinical Pharmacology (12.3)*]. Therefore, the recommended

maximum dosage of NOURIANZ in patients concomitantly using strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, clarithromycin) is 20 mg once daily [see *Dosage and Administration* (2.2)].

Strong CYP3A4 Inducers

Coadministration of NOURIANZ with a strong CYP3A4 inducer (rifampin) decreased istradefylline C_{max} and AUC_{inf} by 45% and 81%, respectively [see *Clinical Pharmacology* (12.3)]. Therefore, it is recommended to avoid use of NOURIANZ with strong CYP3A4 inducers (e.g., carbamazepine, rifampin, phenytoin, St. John's wort) [see *Dosage and Administration* (2.3)].

7.2 Effect of NOURIANZ on Other Drugs

CYP3A4 Substrates

Coadministration of NOURIANZ 20 mg with a CYP3A4 substrate (midazolam) did not affect the CYP3A4 substrate exposure, while concomitant administration of NOURIANZ 40 mg increased the CYP3A4 substrate (atorvastatin) C_{max} and AUC_{inf} by 1.5-fold [see *Clinical Pharmacology* (12.3)]. Monitor for an increase in adverse reactions of concomitant drugs that are CYP3A4 substrates when coadministering with NOURIANZ 40 mg.

P-glycoprotein (P-gp) Substrates

Coadministration of NOURIANZ with a P-gp substrate (digoxin) increased the P-gp substrate C_{max} and AUC_{inf} by 33% and 21%, respectively [see *Clinical Pharmacology* (12.3)]. Monitor for an increase in adverse reactions of concomitant drugs that are P-gp substrates when coadministering with NOURIANZ.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of NOURIANZ in pregnant women. In animal studies (*see Data*), oral administration of istradefylline during pregnancy resulted in teratogenicity (increased incidences of fetal structural abnormalities, embryofetal and offspring mortality and growth deficits) at clinically relevant exposures and in the absence of maternal toxicity. The teratogenic effects of istradefylline in pregnant rabbits were substantially greater when administered in combination with levodopa/carbidopa than when administered alone.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

Oral administration of istradefylline (0, 40, 200, or 1000 mg/kg/day) to pregnant rats throughout organogenesis resulted in decreased fetal body weight and increased fetal skeletal and visceral variations at the highest dose tested. Plasma exposure (AUC) at the no-effect dose for adverse effects on embryofetal development in rats (200 mg/kg/day) is approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 40 mg.

Oral administration of istradefylline (0, 50, 200, or 800 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in increased embryofetal mortality at the mid and high doses, increased fetal malformations (external, visceral, skeletal) at all doses, and reduced fetal body weight at the highest dose tested. A no-effect dose for adverse effects on embryofetal development in rabbits was not identified. Plasma exposure (AUC) at the lowest dose tested (50 mg/kg/day) is less than that in humans at the MRHD.

In pregnant rabbits, oral administration of istradefylline (0, 50, 200, or 400 mg/kg/day) alone or in combination with oral levodopa/carbidopa (80/20 mg/kg/day) throughout the period of organogenesis resulted in an increase in embryofetal mortality and an increase (marked at the high dose) in malformations (including limb reduction, craniofacial, and cardiovascular) in fetuses from rats administered istradefylline at all doses in combination with levodopa/carbidopa. Istradefylline alone resulted in an increase in embryofetal mortality and visceral malformations; no increase in fetal malformations was observed with levodopa/carbidopa alone. Fetal body weight was reduced by istradefylline alone (400 mg/kg/day) and in combination (200 and 400 mg/kg/day) with levodopa/carbidopa. A no-effect dose for adverse effects on embryofetal development in rabbits when istradefylline was administered in combination with levodopa/carbidopa was not identified. Plasma exposure (AUC) at the lowest dose of istradefylline tested (50 mg/kg/day) in combination with levodopa/carbidopa is less than that in humans at the MRHD.

Oral administration of istradefylline (0, 6, 25, 100, or 400 mg/kg/day) to female rats throughout gestation and lactation resulted in decreased pup survival and reduced pup body weight (which persisted into adulthood) at all but the lowest dose tested. Exposure to drug in the milk may have contributed to these effects, as demonstrated in pups of untreated (control) dams reared by dams receiving istradefylline (400 mg/kg/day). No adverse effects were observed on physical or neurobehavioral development, or reproductive function. Plasma exposure at the no-effect dose for adverse effects on pre- and postnatal development in rats (6 mg/kg/day) is less than that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of istradefylline in human milk, the effects of istradefylline on the breastfed infant, or the effects of istradefylline on milk production. Istradefylline was present in the milk of lactating rats at concentrations up to 10 times that in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NOURIANZ, and any potential adverse effects on the breastfed infant from NOURIANZ or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of NOURIANZ during pregnancy is not recommended. Women of childbearing potential should be advised to use contraception during treatment with NOURIANZ [see *Use in Specific Populations* (8.1)].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No adjustment of NOURIANZ dosage is recommended on the basis of age. Of the total number of PD patients who received NOURIANZ in clinical trials, 53% were ≥ 65 years and 13% were ≥ 75 years of age. No overall differences in effectiveness were observed between these patients and younger patients.

8.6 Renal Impairment

No adjustment of NOURIANZ dosage is needed in patients with mild renal impairment (estimated creatinine clearance (CrCL) by Cockcroft-Gault equation: 60-89 mL/min), moderate renal impairment (CrCL 30-59 mL/min), or severe renal impairment (CrCL 15-29 mL/min). NOURIANZ has not been evaluated in patients with end-stage renal disease (ESRD) (CrCL < 15 mL/min) or ESRD requiring hemodialysis [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No adjustment of NOURIANZ dosage is needed in patients with mild hepatic impairment (Child-Pugh Class A).

In patients with moderate hepatic impairment (Child-Pugh B), the steady-state exposures (AUC_{0-24h}) were predicted to be 3.3-fold higher than in healthy subjects, based on the estimated mean terminal half-life. Therefore, the maximum recommended dosage of NOURIANZ in patients with moderate hepatic impairment (Child-Pugh B) is 20 mg once daily [see *Clinical Pharmacology (12.3)*]. Closely monitor patients with moderate hepatic impairment for adverse events when on NOURIANZ treatment [see *Adverse Reactions (6.1)*].

NOURIANZ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Avoid use of NOURIANZ in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

8.8 Tobacco Smokers

Tobacco smoking decreased NOURIANZ steady-state systemic exposures by 38% to 54% [see *Clinical Pharmacology (12.3)*], which may decrease efficacy. Therefore, the recommended NOURIANZ dosage in patients who smoke 20 or more cigarettes per day (or the equivalent amount of another tobacco product) is 40 mg once daily.

10 OVERDOSAGE

10.1 Human Experience

There is limited clinical experience regarding human overdosage with NOURIANZ. In clinical trials, one patient took 6 tablets (120 mg, 3 times the maximum recommended dosage) of istradefylline with alcoholic beverages and developed hallucinations, agitation, and worsening dyskinesia.

10.2 Management of Overdose

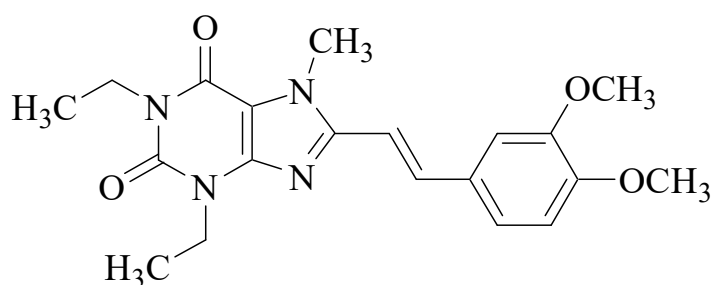
There are no known specific antidotes for NOURIANZ nor any specific treatment for istradefylline overdose. If an overdose occurs, NOURIANZ treatment should be discontinued and supportive

treatment should be administered as clinically indicated. Consider the long terminal half-life of istradefylline (about 83 hours) and the possibility of multiple drug involvement.

Consult a Certified Poison Control Center for up-to-date guidance and advice.

11 DESCRIPTION

NOURIANZ contains istradefylline, an adenosine receptor antagonist, which has a xanthine derivative structure. The chemical name is (*E*)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione. Its molecular formula is C₂₀H₂₄N₄O₄. The molecular weight is 384.43. Istradefylline has the following structural formula:



Istradefylline is a light yellow-green crystalline powder. Istradefylline has a dissociation constant (pK_a) of 0.78. The aqueous solubility of istradefylline is ~0.5 µg/mL across the physiological pH range and 0.6 µg/mL in water.

NOURIANZ tablets are intended for oral administration only. Each tablet contains 20 mg or 40 mg of istradefylline and the following inactive ingredients: crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polyvinyl alcohol. The film coating contains hypromellose, lactose monohydrate, polyethylene glycol 3350, titanium dioxide, triacetin, and the following dyes: iron oxide red and iron oxide yellow. Carnauba wax is used for polishing.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which istradefylline exerts its therapeutic effect in Parkinson disease is unknown. In *in vitro* studies and in *in vivo* animal studies, istradefylline was demonstrated to be an adenosine A_{2A} receptor antagonist.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NOURIANZ (40 mg or 160 mg [4 times the maximum recommended dosage] once daily for 14 days) on the QTc interval was evaluated in a randomized, placebo and moxifloxacin-controlled, multiple-dose, blinded, parallel group study. There was no clinically significant prolongation of QTc interval or relationship between changes in QTc and concentrations of istradefylline.

12.3 Pharmacokinetics

Istradefylline exhibits dose-proportional pharmacokinetics after multiple oral doses from 20 mg to 80 mg (2 times the maximum recommended dosage). Steady-state was reached within 2 weeks of once-daily dosing. The pharmacokinetics of istradefylline were similar in PD patients and healthy subjects.

Absorption

The median time to reach the maximum concentration (T_{max}) for istradefylline was about 4 hours under fasted dosing conditions.

Effect of Food

Istradefylline exposure, represented by the area under the curve over time to infinity (AUC_{inf}), increased 1.25-fold when NOURIANZ was coadministered with a standard high-fat meal, compared with administration in a fasted state. Istradefylline maximum plasma concentrations (C_{max}) increased by 1.64-fold and T_{max} was shortened by 1 hour when NOURIANZ was administered with a high-fat meal. These differences in pharmacokinetic parameters are not expected to be clinically significant [see *Dosage and Administration (2.1)*].

Distribution

The plasma protein binding of istradefylline was approximately 98%. The apparent volume of distribution (V_d/F) of istradefylline is approximately 557 liters.

Elimination

The total clearance of istradefylline is approximately 4.6 L/hour. The mean terminal half-life ($t_{1/2}$) for istradefylline at steady-state is approximately 83 hours.

Metabolism

In humans, istradefylline is exclusively eliminated via metabolism. *In vitro* studies indicate that istradefylline is primarily metabolized via CYP1A1 and CYP3A4, with minor contribution from CYP1A2, 2B6, 2C8, CYP2C9, CYP2C18, and 2D6. Six metabolites have been identified in human plasma. These metabolites each account for less than 10% of the exposure of the parent drug.

Excretion

Approximately 48% of a 40-mg oral dose of ^{14}C -istradefylline was eliminated in feces, and 39% in urine. Unchanged istradefylline was not detected in urine.

Specific Populations

In patients with moderate hepatic impairment (Child-Pugh B), the steady-state exposure (AUC_{0-24}) of istradefylline is predicted to be 3.3-fold higher relative to healthy subjects, based on the estimated mean terminal half-life [see *Use in Specific Populations (8.7)*]. Based on population pharmacokinetic analyses, no clinically relevant changes in the pharmacokinetics of istradefylline were observed based on age, sex, weight, or race. No clinically relevant changes in istradefylline exposure were observed in patients with severe renal impairment (CrCL 15-29 mL/min) or mild hepatic impairment. NOURIANZ has not been studied in patients with ESRD (CrCL < 15 mL/min), ESRD patients requiring hemodialysis, or severe hepatic impairment (Child-Pugh C) [see *Use in Specific Populations (8.6, 8.7)*].

Steady-state systemic exposure to istradefylline (40 mg) is 38% to 54% lower in tobacco smokers (who smoke 20 or more cigarettes per day) when compared with non-smokers matched for age, gender, and body weight [see *Specific Populations (8.8)*].

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Drug-Metabolizing Enzyme Inhibition

Istradefylline is a weak inhibitor of CYP3A4, but not an inhibitor of CYP1A2, 2B6, 2C9, 2C19, or 2D6 *in vitro*.

Drug-Metabolizing Enzyme Induction

Istradefylline was a weak inducer of CYP3A4 but not an inducer of CYP1A2 and 2B6 when tested *in vitro*. However, clinical drug-drug interaction studies with a CYP3A4 substrate (i.e., midazolam) showed no induction of CYP3A4.

Transporters

Istradefylline was not a substrate for drug transporters P-gp, BCRP, OATP1B1, or OATP1B3 when tested *in vitro*. Istradefylline was a weak inhibitor for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OCT2, MATE1, and MATE2-K, but not an inhibitor of OAT3 when tested *in vitro*.

In Vivo Assessment of Drug Interactions

Effect of Other Drugs on Istradefylline

Strong CYP3A4 Inhibitors

Coadministration of ketoconazole (200 mg twice daily for 4 days) with a single dose of istradefylline (40 mg) increased the AUC_{inf} of istradefylline by 2.5-fold, but had no effect on C_{max} [see *Drug Interactions (7.1)*].

Strong CYP3A4 Inducers

Coadministration of rifampin (600 mg daily for 20 days) with a single dose of istradefylline (40 mg) reduced the C_{max} and AUC_{inf} of istradefylline by 45% and 81% respectively, when compared with istradefylline administered alone [see *Drug Interactions (7.1)*].

Effect of Istradefylline on Other Drugs

CYP3A4 Substrates

Coadministration of istradefylline at higher than the recommended doses (80 mg for 14 days) with a single dose of midazolam (10 mg) increased midazolam AUC_{inf} 2.4-fold, and C_{max} by 1.6-fold, when compared with midazolam administered alone. Coadministration of lower doses of istradefylline (5 mg and 20 mg) with midazolam (7.5 mg) did not have these effects [see *Drug Interactions (7.2)*].

Coadministration of istradefylline (40 mg daily for 17 days) with a single dose of atorvastatin (40 mg) increased the C_{max} and AUC_{inf} of atorvastatin by 1.5-fold, compared with atorvastatin alone [see *Drug Interactions (7.2)*].

P-glycoprotein Substrates

Coadministration of istradefylline (40 mg daily for 21 days) with a single dose of digoxin (0.4 mg) increased the C_{max} and AUC_{inf} of digoxin by 33% and 21%, respectively, when compared with digoxin alone [see *Drug Interactions (7.2)*].

Carbidopa/Levodopa

Coadministration of istradefylline (80 mg [two times the recommended maximum dosage] daily for 14 days) with a single dose of carbidopa/levodopa (50/200 mg) did not affect the pharmacokinetics of carbidopa/levodopa. Also, coadministration of istradefylline (20 mg or 40 mg daily for 14 days) with carbidopa/levodopa (25/100 mg three times a day for 14 days) did not affect the systemic exposure of carbidopa/levodopa.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In lifetime oral carcinogenicity studies, there was no evidence of carcinogenicity in mouse (0, 25, 125, or 250 mg/kg) or rat (0, 30, 100, or 320 mg/kg). Plasma exposures (AUC) at the highest doses tested were approximately 20 (mouse) and 10 (rat) times that in humans at the maximum recommended human dose (MRHD) of 40 mg/day.

Mutagenesis

Istradefylline was negative in *in vitro* (bacterial reverse mutation assay, chromosomal aberration in mammalian cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Oral administration of istradefylline (0, 160, 360, or 800 mg/kg/day) to male and female rats prior to and during mating and continuing in females to gestation day 7 resulted in a decrease in fertility at the highest dose tested and an increase in preimplantation loss at the mid and high doses. Sperm motility was reduced at the highest dose tested. Plasma exposure (AUC) at the no-effect dose (160 mg/kg for adverse effects on reproductive function is approximately 3 times that in humans at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

Oral administration of istradefylline (0, 30, 100, or 320 mg/kg/day) to rats for two years resulted in an increase in the incidence and severity of vascular mineralization in the brain (including in the caudate/putamen, globus pallidus, thalamus, and nucleus accumbens) at all doses tested. The vascular mineralization was composed of calcium and phosphorus and, at higher doses, were reported to partially or completely occlude the blood vessels. There was no evidence of neuronal degeneration, inflammation, or glial response associated with the foci of mineralization.

Brain mineralization was not detected in mice administered istradefylline (0, 25, 125, or 250 mg/kg/day) orally for two years or in dogs administered istradefylline (0, 10, 30, or 100 mg/kg/day) orally for 52 weeks.

14 CLINICAL STUDIES

The efficacy of NOURIANZ for the adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes was shown in four randomized, multicenter, double-blind, 12-week, placebo-controlled studies (Study 1, NCT00456586; Study 2, NCT00199407; Study 3, NCT00455507; and Study 4, NCT00955526). The studies enrolled patients with a mean duration of Parkinson's disease of 9 years (range: 1 month to 37 years) that were Hoehn and Yahr Stage II to IV, experiencing at least 2 hours (mean approximately 6 hours) of "off" time per day, and were treated with levodopa for at least one year, with stable dosage for at least 4 weeks before screening (mean

total daily dosage range: 416 to 785 mg). Patients continued levodopa treatment with or without concomitant PD medications, including dopamine agonists (85%), COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%), provided the medications were stable for at least 4 weeks before screening and throughout the study period. The studies excluded patients who had received a neurosurgical treatment for PD (e.g., pallidotomy, thalamotomy, deep brain stimulation).

The primary efficacy endpoint was the change from baseline in the daily awake percentage of “off” time, or the change from baseline in total daily “off” time, based on 24-hour diaries completed by patients. A change from baseline in “on” time without troublesome dyskinesia (i.e., “on” time without dyskinesia plus “on” time with non-troublesome dyskinesia) was a secondary efficacy endpoint.

Study 1 was conducted in the U.S. and Canada, and Study 2 was conducted in the U.S. In these studies, patients were randomized to once-daily treatment with NOURIANZ 20 mg, 40 mg, or placebo. Patients treated with NOURIANZ 20 mg or NOURIANZ 40 mg once daily experienced a statistically significant decrease from baseline in percentage of daily awake “off” time, compared with patients on placebo, as summarized in Table 2.

Table 2: Studies 1 and 2: Change From Baseline in Daily Awake OFF Time

	Baseline		Change from Baseline to Endpoint	
	N	(mean ± SD) % of awake “off” hours	N	(LSMD* vs. placebo), % awake “off” hours, (p-value)
Study 1				
Placebo	66	37.2 ± 13.8	65	--
NOURIANZ 40 mg	129	38.4 ± 16.2	126	- 6.78 (<i>p</i> =0.007)
Study 2				
Placebo	113	38.7 ± 11.6	113	--
NOURIANZ 20 mg	112	39.8 ± 14.0	112	- 4.57 (<i>p</i> =0.025)

* LSMD: Least squares mean difference; a negative value indicates a greater reduction from baseline in Percentage Daily Awake “off” time for NOURIANZ, relative to placebo.
SD: Standard Deviation

Compared with patients on placebo, patients treated with NOURIANZ experienced an additional increase from baseline in “on” time without troublesome dyskinesia of 0.96 hours (nominal *p*=0.026) in Study 1, and of 0.55 hours (nominal *p*=0.135) in Study 2.

Study 3 and Study 4 were conducted in Japan. In these studies, patients were randomized equally to treatment with NOURIANZ 20 mg, 40 mg, or placebo. Patients treated with NOURIANZ 20 mg or NOURIANZ 40 mg once daily experienced a statistically significant decrease from baseline in “off” time compared with patients on placebo, as summarized in Table 3.

Table 3: Studies 3 and 4: Change From Baseline in Daily OFF Time

	Baseline		Change from Baseline to Endpoint	
	N	(mean ± SD) hours	N	(LSMD* vs. placebo) hours (p-value)
Study 3				
Placebo	118	6.4 ± 2.7	118	--
NOURIANZ 20 mg	115	6.8 ± 2.9	115	-0.65 (p=0.028)
NOURIANZ 40 mg	124	6.6 ± 2.5	124	-0.92 (p=0.002)
Study 4				
Placebo	123	6.3 ± 2.5	123	--
NOURIANZ 20 mg	120	6.6 ± 2.7	120	-0.76 (p=0.006)
NOURIANZ 40 mg	123	6.0 ± 2.5	123	-0.74 (p=0.008)

* LSMD: Least squares mean difference; a negative value indicates a greater reduction from baseline in “off” time for NOURIANZ, relative to placebo.

SD: Standard Deviation

In Study 3, compared with placebo, an additional increase from baseline in “on” time without troublesome dyskinesia of 0.57 hours (nominal $p=0.085$) and of 0.65 hours (nominal $p=0.048$), respectively, were observed in patients treated with NOURIANZ 20 mg or NOURIANZ 40 mg. In Study 4, the corresponding increases in “on” time without troublesome dyskinesia were 0.83 hours (nominal $p=0.008$) for NOURIANZ 20 mg and 0.81 hours (nominal $p=0.008$) for NOURIANZ 40 mg.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NOURIANZ (istradefylline) tablets are available as:

20 mg Tablets:

Peach-colored, pillow-shaped, film-coated tablets with “20” debossed on one side.
Bottle of 90: NDC 42747-602-90

40 mg Tablets:

Peach-colored, almond-shaped, film-coated tablets with “40” debossed on one side.
Bottle of 90: NDC 42747-604-90

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dyskinesia

Advise patients that NOURIANZ may cause dyskinesia or exacerbate pre-existing dyskinesia [*see Warnings and Precautions (5.1)*].

Hallucinations / Psychotic Behavior

Advise patients that NOURIANZ may cause hallucinations or psychotic behavior and they should report any of these adverse reactions to their healthcare provider [*see Warnings and Precautions (5.2)*].

Impulse Control / Compulsive Behaviors

Inform patients that they may experience intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking NOURIANZ and one or more medication(s) for the treatment of Parkinson's disease (including levodopa). Advise patients that they should report any of these adverse reactions to their healthcare provider [*see Warnings and Precautions (5.3)*].

Concomitant Medications

Certain medications can cause an interaction with NOURIANZ. Advise patients to inform their healthcare provider about their smoking status and about all of the medicines they are taking or plan to take, including over-the-counter medicines, dietary supplements, and herbal products [*see Drug Interactions (7.1, 7.2) and Use in Specific Populations (8.8)*].

NOURIANZ[®] (istradefylline)

Manufactured by:

Kyowa Kirin, Inc.

Bedminster, NJ 07921