PDL DRUG REVIEW

Proprietary Name: Nourianz®
Common Name: istradefylline
PDL Category: Anti-Parkinsonian Drugs

Comparable Products	Preferred Drug List Status
Entacapone	Preferred
Rasagiline	Non-Preferred
Selegiline	Preferred
Xadago	Non-Preferred

Summary

Pharmacology/Usage: Istradefylline, the active ingredient of Nourianz®, is an adenosine receptor antagonist, which has a xanthine derivative structure. The mechanism of action by which it exerts its therapeutic effects in Parkinson disease is not known. In *in vitro* and *in vivo* animal studies, istradefylline was demonstrated to be an adenosine A2A receptor antagonist.

Indication: As adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risk associated with use in pregnant women. In animal studies, oral administration of istradefylline during pregnancy resulted in teratogenicity at clinically relevant exposures and in the absence of maternal toxicity. The teratogenic effects of istradefylline in pregnant rabbits were substantially greater when given in combination with levodopa/carbidopa than when given alone. Use during pregnancy is not recommended. Women of childbearing potential should be advised to use contraception during treatment with Nourianz®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 20mg, 40mg

Recommended Dosage: Take 20mg PO QD, and this dose may be increased to a maximum of 40mg QD, based on individual need and tolerability. Initial dose titration is not required and Nourianz® can be taken with or without food.

The recommended dose in patients who use tobacco in amounts of 20 or more cigarettes per day (or the equivalent amount of another tobacco product) is 40mg QD.

Dose adjustments are not required with mild hepatic impairment. The maximum recommended dose in patients with moderate hepatic impairment is 20mg QD. Closely monitor for adverse reactions. Use should be avoided with severe hepatic impairment. Dose adjustments are not required with renal impairment; however, use has not been assessed in patients with end-stage renal disease (ESRD) or ESRD requiring hemodialysis.

Drug Interactions: Co-administration of Nourianz® with a strong CYP3A4 inhibitor (ketoconazole) increased istradefylline AUC. Thus, the recommended maximum dosage of Nourianz® in patients concomitantly using strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, clarithromycin) is 20mg QD. Co-administration of Nourianz® with a strong CYP3A4 inducer (rifampin) decreased istradefylline Cmax and AUC. Thus, it is recommended to avoid use of Nourianz® with strong CYP3A4 inducers (e.g. carbamazepine, rifampin, phenytoin, St. John's wort). Co-administration of Nourianz® 20mg with a CYP3A4 substrate (midazolam) did not affect the CYP3A4 substrate exposure, while concomitant administration of Nourianz® 40mg increased the CYP3A4 substrate (atorvastatin) Cmax and AUC. Monitor for an increase in adverse reactions of concomitant drugs that are CYP3A4 substrates when co-administering with Nourianz® 40mg. Last, co-administration of Nourianz® with a

P-gp substrate (digoxin) increased the P-gp substrate Cmax and AUC. Monitor for an increase in adverse reactions of concomitant drugs that are P-gp substrates when co-administering with Nourianz®.

Box Warning: There are no box warnings listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Nourianz® 20mg/40mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included dyskinesia (7%/9%), dizziness (0%/2%), constipation (2%/3%), nausea (0%/1%), diarrhea (0%/1%), hallucination (0%/3%), insomnia (0%/2%), decreased appetite (0%/2%), blood alkaline phosphatase increased (0%/1%), blood glucose increased (1%/2%), blood urea increased (1%/2%), upper respiratory tract inflammation (1%/2%), and rash (0%/1%).

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

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®.

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 eat compulsively, and/or experience other intense urges, and have inability to control these urges. In some post-marketing cases, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. As patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or caregivers about the development of new or increased 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®.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Kyowa Kirin, Inc

Analysis: The safety and efficacy of Nourianz® for the adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes was shown in 4 randomized, multicenter, double-blind, placebo-controlled, 12-week studies. Patients enrolled in the studies had 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 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 785mg). Patients continued levodopa treatment with or without concomitant Parkinson's disease (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 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 US and Canada, while study 2 was conducted in the US. Results suggested that patients treated with Nourianz® 20mg or Nourianz® 40mg QD experienced a statistically significant decrease from baseline in percentage of daily awake "off" time compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Baseline		Change from baseline to endpoint	
	N	% of awake 'off' hours, mean	N	% awake 'off' hours, least square mean difference vs placebo (p-value)
Study 1				
Placebo	66	37.2	65	

	Baseline		Change from baseline to endpoint	
	N	% of awake 'off' hours, mean	N	% awake 'off' hours, least square mean difference vs placebo (p-value)
Nourianz® 40mg	129	38.4	126	-6.78 (p=0.007)
Study 2				
Placebo	113	38.7	113	
Nourianz® 20mg	112	39.8	112	-4.57 (p=0.025)

Compared with the placebo group, the Nourianz® group 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 4 were conducted in Japan. In these studies, patients were randomized equally to treatment with Nourianz® 20mg, 40mg, or placebo. Results suggested that patients treated with Nourianz® 20mg or Nourianz® 40mg experienced a statistically significant decrease from baseline in "off" time compared with patients on placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Baseline		Change from baseline to endpoint	
	N	hours, mean	N	hours, least square mean difference vs placebo (p-value)
Study 3				
Placebo	118	6.4	118	
Nourianz® 20mg	115	6.8	115	-0.65 (p=0.028)
Nourianz® 40mg	124	6.6	124	-0.92 (p=0.002)
Study 4				
Placebo	123	6.3	123	
Nourianz® 20mg	120	6.6	120	-0.76 (p=0.006)
Nourianz® 40mg	123	6.0	123	-0.74 (p=0.008)

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 seen in patients treated with Nourianz® 20mg or Nourianz® 40mg. In study 4, the corresponding increases in "on" time without troublesome dyskinesia were 0.83 hours (nominal p=0.008) for Nourianz® 20mg and 0.81 hours (nominal p=0.008) for Nourianz® 40mg.

Place in Therapy: Nourianz® is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "off" episodes. In clinical trials compared with placebo, patients treated with Nourianz® experienced a statistically significant decrease from baseline in percentage of daily awake "off" time and in "off" time.

There is no evidence at this time that Nourianz® is safer or more effective than the currently preferred medications. It is therefore recommended that Nourianz® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1]Nourianz [package insert]. Bedminster, NJ: Kyowa Kirin, Inc; 2019.