CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	22075
PDUFA Goal Date	August 27, 2019
OSE RCM #	2019-489
Reviewer Name(s)	Yasmeen Abou-Sayed, PharmD.
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	August 26, 2019
Subject	Evaluation of Need for a REMS
Established Name	istradefylline
Trade Name	Nourianz
Name of Applicant	Kyowa Kirin Inc.
Therapeutic Class	Adenosine A2A receptor antagonist
Formulation(s)	20 and 40 mg oral tablets
Dosing Regimen	20 mg once daily, may be increased to 40 mg

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Nourianz (istradefylline) is necessary to ensure the benefits outweigh its risks. Kyowa Kirin submitted New Drug Application (NDA) 022075, a response to a Not Approvable letter issued on February 25, 2008, due to a lack of demonstrated efficacy and non-inferiority to approved products.[1,2] The proposed indication is for adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes. The risk associated with istradefylline is dyskinesia. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK has determined that a REMS is not needed to ensure the benefits of istradefylline outweigh its risks. The safety profile of istradefylline is similar to currently approved therapies used concomitantly with carbidopa/levodopa to treat Parkinson's disease. The most significant risk associated with istradefylline is dyskinesia, an adverse event common other drugs used concomitantly with carbidopa/levodopa to treat PD patients. Overall, istradefylline, given adjunctively to carbidopa/levodopa, and with other conventional PD medications, is well tolerated with an acceptable safety profile in subjects with PD. Safety concerns associated with istradefylline can be communicated though labeling.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nourianz (istradefylline) is necessary to ensure the benefits outweigh its risks. Kyowa Kirin submitted New Drug Application (NDA) 022075, a response to a Not Approvable letter issued on February 25, 2008, for istradefylline with a proposed indication for adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes. This application is under review in the Division of Neurology Products (DNP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Nourianz (istradefylline), a new molecular entity (NME)[a], is an adenosine A2A receptor inhibitor proposed for adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes. Adenosine A2A receptor activation increases the excitability of the indirect pathway via adenosine A2A receptors in the striatum and globus pallidus. Blockade of adenosine A2A receptors results in a decrease in excessive activation of the indirect pathway resulting in restoration of the balance in the basal ganglia thalamocortical circuit and provides an alternative, non-dopaminergic approach to symptomatic relief of Parkinson's disease.[3] Istradefylline is proposed as a 20 mg and 40 mg oral tablet, to be taken as a maintenance drug, once daily at a dose of 20 mg, which

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

may be increased to 40 mg if tolerated.[b] Istradefylline was approved in Japan in 2013 for the proposed indication.

2.2 REGULATORY HISTORY:

The following is a summary of the regulatory history for NDA 022075 relevant to this review:

- 3/29/07: Applicant submitted NDA 022075 for the indication of adjunctive therapy to levodopa and carbidopa in the treatment of Parkinson's disease.
- 2/25/08: Applicant received a Not Approvable letter for NDA 022075, citing a lack of demonstrated efficacy and non-inferiority to products approved at the time.
- 2/27/2019: Applicant resubmitted NDA 022075 for the indication of adjunctive treatment to levodopa/carbidopa in patients with Parkinson's Disease (PD) who experience "OFF" episodes.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative condition caused by the loss of dopamine-producing neurons in the nigrostriatal pathway of the brain, which leads to four classical primary symptoms: bradykinesia, tremor, muscle rigidity, and postural instability. Psychiatric manifestations, which include depression and visual hallucinations, are common, but not uniformly present, and dementia eventually occurs in at least 20% of cases. Parkinson's disease begins between the ages of 45 and 70. An estimated 4% of PD patients are diagnosed before the age of 50, and the incidence increases with age; and is more common in men than women. PD affects an estimated one million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years.[c] Parkinson's disease affects more than the number of people diagnosed with multiple sclerosis, muscular dystrophy, and Lou Gehrig's disease combined. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients' social life, family, quality of life, work, and health.[d,4]

The mainstay of the treatment for Parkinson's disease is pharmacologic replacement of dopamine in the form of levodopa, which is converted to dopamine once it enters the brain. Levodopa, however, is associated with incapacitating motor fluctuations and dyskinesias. Other dopaminergic treatments have

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

been added to clinical practice to reduce or delay the need for levodopa therapy, improve the efficacy of levodopa, or moderate its adverse effects. Other effective agents include dopamine agonists, inhibitors of catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B), anticholinergics, and amantadine. As the disease progresses, patients may notice fluctuations between "on" periods, when they experience a good response to medication, and "off" periods, when the benefit from medications wears off and symptoms re-emerge.[5] Treatment of advanced or disabling symptoms includes neurosurgical procedures, such as deep brain stimulation of the subthalamic nucleus or globus pallidus. Occupational, physical, and speech therapy are often helpful."[6]

In the early stages of PD, it is recommended that younger subjects delay the initiation of levodopa therapy, and, instead, start treatment with a dopamine agonist or MAO-B inhibitor. Inhibition of monoamine oxidase type B (MAO-B), the major enzyme metabolizing dopamine in the human brain, may help conserve the depleted supply of dopamine at synaptic levels, and delay the need for exogenous levodopa.[7] However, as their disease progresses, the majority of subjects will require combination treatment to optimize their dopaminergic therapy. Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement or delay the use of established dopaminergic therapies. Appendix A is a summary of approved U.S. drugs for treating PD.

4 Benefit Assessment

In the initial NDA submission, the Agency was unable to conclude substantial efficacy of istradefylline based on five pivotal trials submitted at the time.[8,9]

The current submission of NDA 22075 includes 3 pivotal trials, one phase 2 (6002-0608 [National Clinical Trial (NCT) 00455507]) and two phase 3 confirmatory double-blind, placebo-controlled studies (6002-009 [NCT00955526] and 6002-014 [NCT02610231]) in patients with Parkinson's Disease.[10] All three studies were multi-center studies and study subjects were on a stable levodopa/carbidopa regimen. Patients were required to be on at least 300 mg of levodopa daily in studies 6002-0608 and 6002-009, and a minimum of 400 mg in Study 6002-014. All three studies had a similar design and included two dose levels of study drug: 20 mg and 40 mg tablets administered once daily for 12 weeks. The primary efficacy endpoint studied in all three studies was the total number of hours awake time per day spent in the "OFF" state. While two of the three studies (0608 and 009, both conducted in Japan) showed statistically significant reduction in the primary efficacy endpoint – total number of hours of awake time per day spent in the "OFF"-state compared to placebo, the third study (US patients, 014) failed to demonstrate a statistically significant reduction in the primary efficacy endpoint compared to placebo. With regard to secondary endpoints, including an increase in 'ON' time with or without troublesome dyskinesia, total daily hours asleep, and subject ratings on the Unified Parkinson's Disease Rating Scale[e], most results were not statistically significant and do not provide support to the primary endpoint.[11]

[e] The Unified Parkinson's Disease Rating Scale (UPDRS) is a validated tool used to assess the functional status of subjects with Parkinson's disease. Subjects provide historical information on activities of daily living

Table 1 – Results in pivotal trials for primary efficacy endpoint

Study	Change from Baseline for OFF Time	
	20 mg	40 mg
6002-0608 (Japan) n = 363	-0.62 hours; p=0.028	-0.95 hours; p=0.002
6002-009 (Japan) n = 373	-0.76 hours; p=0.006	-0.74 hours; p=0.008
6002-014 (Multi-national) n = 613	-0.32 hours; p=0.156	0.27 hours; p=0.234

The clinical reviewer has concluded that evidence of efficacy from trials 6006-0608 and 6002-009, conducted in Japan, do not provide sufficient evidence of proof of efficacy in US patients, based on the failure of study 6002-014.[9] Therefore, the clinical reviewer does not support approval. However, the Division of Neurology Products will recommend approval of istradefylline, based on the assessment that the information from studies 0608 and 009 support the conclusion that Nourianz 20 mg/day and 40 mg/day are effective for reducing Off time in patients with PD.[12,f]

5 Risk Assessment & Safe-Use Conditions

Istradefylline has been evaluated in 3,423 subjects in a total of 23 Phase 2 and 3 studies, with 2,933 of those subjects receiving istradefylline as adjunctive treatment for PD. Additionally, approximately 56,000 patients in Japan have taken istradefylline in the post-marketing setting.[13] A total of 1,172 subjects were exposed to istradefylline for 1 year or longer. One long-term, open-label Phase 3 study (Study 6002-018) was completed after this submission, and data from it was not included in the safety analysis. Table 3 lists the different studies included in the safety database and separates them into Pools for ease of classifying adverse events.

*Long-term open-label Phase 3 study (Study 6002-018), and Phase 1 studies not included in above pools

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

A total of 37 deaths occurred in the safety population, with 32 subjects in the istradefylline group, and 5 subjects in the placebo group. Seven deaths were considered related to study drug included. All the istradefylline treated subjects who died had significant confounding medical history or concurrent medical conditions, therefore no conclusion can be made as to whether these deaths were definitively associated with istradefylline treatment.[14]

Most adverse events (AEs) experienced by study subjects were mild to moderate in severity. The most common treatment emergent adverse events occurring in 2% or more of the istradefylline group are in the table below, with the most prevalent adverse event of special interest being dyskinesia:

Table 3 – Treatment emergent adverse events

Preferred Term	Percent of Subjects				
	Placebo; n=1010	Istradefylline (mg/day)			
		10; n = 153	20; n = 869	40; n = 896	60; n=155
Dyskinesia	10	22	16	18	24
Nausea	5	7	6	6	23
Dizziness	4	5	5	5	14
Constipation	3	7	6	5	2
fall	5	6	4	5	5
Insomnia	4	7	4	5	3
Worsening of PD	4	11	4	3	3
Viral upper respiratory tract infection	3	3	4	3	2
Headache	3	5	3	3	5
Back pain	3	4	3	3	6
Arthralgia	3	6	2	2	8
Hallucination	2	1	2	3	6

The incidence of AEs that are known to occur with levodopa and other dopaminergic drugs was similar for istradefylline and placebo.[g] These AEs include, in particular, orthostatic hypotension, cardiac events, sleep attack, and psychiatric manifestations such as psychotic disorder, psychosis, somnolence, anxiety, confusion, depression, and impulse control disorders.

According to the Applicant, post-marketing reports did not reveal any additional safety signals for istradefylline and are consistent with findings from the clinical studies.[11] The Division of Neurology Products review of the additional safety information included in the resubmission concurs with this assessment.[12]

5.1 ADVERSE EVENTS OF SPECIAL INTEREST

5.1.1 Dyskinesia

Within the safety pool, the incidence of new onset or exacerbated dyskinesia was reported as an adverse reaction in 12% of the subjects receiving 20 mg istradefylline and 15% of the subjects receiving 40 mg istradefylline, versus 7% for placebo. The majority of dyskinesia was mild or moderate in severity, and the reported mean onset of dyskinesia was 16 days after starting istradefylline. The incidence of dyskinesia causing study discontinuation was 1% in the 20 mg group, 0% in the 40 mg group, and 0% for placebo. Dyskinesia is an AE commonly experienced in this population, both due to carbidopa/levodopa treatment, and other concomitant treatments currently used in the treatment of PD. Safety concerns associated with dyskinesia will be communicated via warnings and precautions in the prescribing information.

6 Expected Postmarket Use

If approved in the United States, istradefylline is likely to be prescribed by neurologists and movement disorder specialists. These prescribers should be familiar with the risk of dyskinesia associated with other drugs used concomitantly with carbidopa/levodopa to treat PD patients. It is expected that the drug will be used in both an in-patient and out-patient setting. Patients with PD are likely to self-medicate, taking the tablets by mouth as directed by their healthcare provider. Patients with more advanced PD may not be able to self-medicate and are likely to necessitate dispensation and/or administration of istradefylline under the supervision of a caregiver.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for istradefylline beyond routine pharmacovigilance and labeling.[15]

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The Division of Neurology Products recommends approval of istradefylline, based on the assessment that the information from studies 0608 and 009 support the conclusion that Nourianz 20 mg/day and 40 mg/day are effective for reducing Off time in patients with PD.[12] Parkinson's disease is a progressive neurodegenerative disease that affects an estimated 1 million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients' social life, family, quality of life, work, and health. The mainstay of treatment is pharmacologic replacement of dopamine in the form of levodopa. However, not only do the therapeutic effects of levodopa start to wear off, it is also associated with incapacitating motor fluctuations and dyskinesias. As the disease progresses, the majority of PD patients will require combination treatment to optimize their therapy. In patients taking levodopa who experience response fluctuations, istradefylline may be effective to produce less OFF time and provide better symptom control, with minimal added risk. There is an increasing demand for new agents to supplement or delay the use of established dopaminergic therapies.

Based on results of two pivotal studies, istradefylline 20 mg and 40 mg demonstrated safety and efficacy for decreasing 'OFF' time without troublesome dyskinesia in patients with Parkinson's Disease per the Division of Neurology Products.

Overall, istradefylline, given adjunctively to carbidopa/levodopa, and with other conventional PD medications, is well tolerated with an acceptable safety profile in subjects with PD. The safety profile of istradefylline is similar to other approved therapies used concomitantly with carbidopa/levodopa to treat Parkinson's disease. The most significant risk observed in istradefylline study subjects was dyskinesia, an adverse event common to drugs used concomitantly with carbidopa/levodopa to treat Parkinson's disease. Prescribers of istradefylline should be familiar with this risk, due to its commonality with other approved therapies for PD. Safety concerns associated with istradefylline will be communicated though the prescribing information.

DRISK agrees that the adverse event profile of the drug does not warrant risk mitigation beyond labeling. Based on the currently available data, DRISK and DNP concur that a REMS is not necessary to ensure the benefits of istradefylline outweigh the risks.

9 Conclusion & Recommendations

The benefit-risk profile is favorable therefore, a REMS is not necessary for istradefylline to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 Appendix A - Drugs approved in the US for Treating Parkinson's Disease

Name (Generic) *Year of Approval*	Dosing	Important Safety and Tolerability Issues	Risk Management
Requip; Requip XL (ropinirole) *1997*	0.25 mg TID; titrated up to 8 mg TID	Somnolence, syncope, orthostatic hypotension, hallucinations, psychoses, dyskinesia, impulse control	Labeling
Mirapex; Mirapex ER (pramipexole) *1997*	0.125 mg TID titrated up to max 1.5 mg TID	Somnolence, orthostatic hypotension, impulse control, hallucinations, dyskinesia	Labeling
Neupro (rotigotine) *2012*	2 mg/24 hrs, up to 8mg/24 hrs	Sulfite sensitivity, somnolence, hallucinations/psychosis, hypotension, syncope, impulse control, dyskinesia	Labeling
Azilect (rasagiline) *2009*	0.5 – 1 mg QD	Hypertension, serotonin syndrome, somnolence, hypotension, dyskinesia, hallucinations, impulse control	Labeling
Sinemet; Sinemet CR (carbiodopa/levodopa) *1977*	25/100 mg TID, titrate up to 100/800 mg total daily	Depression, somnolence, hyperpyrexia, confusion, dyskinesia	Labeling
Eldepryl; Emsam; Zelapar (selegiline) *1997*	1.25 mg QD; up to 2.5 mg QD	Hypertension, serotonin syndrome, somnolence, dyskinesia, hallucinations, impulse control	Labeling
Apokyn (apomorphine) *2004*	2 mg, prn	Thrombus formation, pulmonary embolism, nausea/vomiting, somnolence, syncope, falls, hallucinations, dyskinesia, impulse control, coronary events, QT prolongation	Labeling
Comtan (entacapone) *2001*	200 mg, up to 8 times daily	Somnolence, dyskinesia, hyperkinesia, nausea, diarrhea	Labeling
Tasmar (tolcapone) *1998*	100 mg TID, up to 200 mg TID	Acute fulminant liver failure, somnolence, dyskinesia, nausea, sleep disorders, dystonia, anorexia	Labeling, including Boxed Warning
Symmetrel; Gocovri (amantadine)1*966*	100 mg BID, up to 200 mg BID	Death due to acute toxicity, somnolence, suicidality, hallucinations, orthostatic hypotension, impulse control	Labeling
Xadago (safinamide) *2017*	50-100 mg QD	Hypertension, serotonin syndrome, somnolence, dyskinesia, hallucinations, impulse control	Labeling

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