CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022075Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 16, 2019

To: Leonard Kapcala
Division of Neurology Products (DNP)

Stacy Metz, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for NOURIANZ® (istradefylline) tablets, for oral use

NDA: 022075

In response to the DNP consult request dated April 9, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for NOURIANZ® (istradefylline) tablets, for oral use (Nourianz).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DNP (Stacy Metz) on August 7, 2019 and August 8, 2019, respectively, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on August 13, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DNP (Stacy Metz) on August 16, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
08/16/2019 01:14:00 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 13, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 022075
Product Name and Strength:	Nourianz (istradefylline) tablets, 20 mg and 40 mg
Applicant/Sponsor Name:	Kyowa Kirin, Inc.
FDA Received Date:	August 8, 2019
OSE RCM #:	2019-490-2
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 8, 2019 for Nourianz. The Division of Neurology Products (DNP) requested that we review the revised container labels for Nourianz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

We previously recommended that the 'll' in the established name, istradefylline, on the principal display panel (PDP) be presented in un-bolded font to improve readability. On July 30, 2019, Kyowa Kirin stated that the font presentation of the 'll' in the established name on the PDP is consistent with the other letters in the established name.[b] We acknowledge that when the submitted images of the container labels are magnified, the font presentation is consistent.

[a] Little, C. Label and Labeling Review for Nourianz (NDA 022075). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 03. RCM No.: 2019-490-1.
[b] Available in EDR via: \\cdsesub1\evsprod\nda022075\0065\m1\us\6002-rs-nda-corres-to-fda-info-request--18-20190717-en.pdf

Thus, we find the presentation of the established name on the PDP acceptable from a medication error perspective.

Kyowa Kirin implemented all of our other recommendations.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

COLLEEN L LITTLE
08/13/2019 11:36:43 AM

BRIANA B RIDER
08/13/2019 11:56:10 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 12, 2019
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	NOURIANZ (istradefylline)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 022075
Applicant:	Kyowa Kirin, Inc.

1 INTRODUCTION

On February 27, 2019, Kyowa Kirin, Inc., submitted for the Agency's review a New Drug Application (NDA) 022075 NOURIANZ (istradefylline), tablets, for oral use. The proposed indication is adjuctive treatement to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on April 9, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for NOURIANZ (istradefylline), tablets, for oral use.

2 MATERIAL REVIEWED

- Draft NOURIANZ (istradefylline) PPI received on April 9, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 8, 2019.
- Draft NOURIANZ (istradefylline) Prescribing Information (PI) received on April 10, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 7, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
08/12/2019 04:11:24 PM
DMPP-OPDP review of istradefylline (NOURIANZ) NDA 22075 PPI

DHARA SHAH
08/12/2019 04:13:29 PM

MARCIA B WILLIAMS
08/13/2019 10:40:05 AM

LASHAWN M GRIFFITHS
08/13/2019 11:28:18 AM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 6, 2019

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: Istradefylline (KW-6002)
NDA 22,075 (IND 58,356)
Indication: Adjunctive therapy for Parkinson's disease (b) (4)
(b) (4)
Sponsor: Kyowa Hakko Kirin Pharma, Inc.

Materials reviewed: NDA 22075 (February 27, 2019)
Statistical review of human abuse potential study (Ran Bi, Ph.D., Office of Biostatistics, April 23, 2019)

TABLE OF CONTENTS

I. BACKGROUND

The Division of Neurology Products (DNP) requested that CSS conduct an abuse potential assessment of the preclinical and clinical studies conducted with istradefylline under NDA 22075. In 2008, Kyowa Hakko Kirin Pharma, Inc., received a Not Approvable letter for their New Drug Application (NDA), based on a lack of efficacy and the need for clarification of the nonclinical mineralization findings.

CSS did not participate in the review of the NDA during its first submission cycle, but was subsequently consulted by DNP as the Sponsor planned abuse-related studies under IND 58,356. CSS also participated in the pre-NDA meeting on February 7, 2018. The Sponsor resubmitted their NDA on February 27, 2019.

Istradefylline (also known as KW-6002) is a new molecular entity that is a highly selective adenosine A2A receptor antagonist. It is a structural analog of caffeine and a derivative of xanthine. Istradefylline is proposed as an adjunct treatment for patients with (b) (4) Parkinson's disease (PD) who are treated with levodopa/carbidopa and experience (b) (4) off symptoms.

In animals, istradefylline has been shown to potentiate and prolong the effects of levodopa in experimental models of Parkinson's disease. The Sponsor hypothesizes that blockage of the A2A receptors by istradefylline reduces the excitability of this indirect pathway of the basal ganglia, resulting in an improvement in Parkinson's disease symptoms.

The proposed dose of istradefylline is 20 mg administered orally, once a day, with or without food. If a sufficient clinical response is not achieved, the dose may be increased to 40 mg administered once daily.

In March 2013, Japan approved istradefylline (as Nouriast) at 20 and 40 mg/day as an adjunct treatment for PD patients taking levodopa who experienced wearing-off phenomenon. (b) (4)

(b) (4)

In the NDA, the Sponsor concludes that istradefylline does not produce abuse potential or physical dependence. Based on the Sponsor's assessment that istradefylline does not produce abuse potential, they propose that their drug not be scheduled under the Controlled Substances Act.

II. CONCLUSIONS

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 22075 for istradefylline and concludes that the drug has negligible abuse potential and does not require scheduling under the Controlled Substances Act. This conclusion is based on the data described below:

- In receptor binding and functional studies, istradefylline has highly selective activity at adenosine A2A receptors as an antagonist. This is the same mechanism of action as the unscheduled stimulant, caffeine. It does not have affinity for any sites associated with scheduled drugs of abuse.

- In general behavior tests, istradefylline produced dose-dependent increases in locomotor activity. This would be expected from a drug with caffeine-like effects.

- In a drug discrimination study, istradefylline did not generalize to the cue produced by amphetamine (a dopamine releaser). This would be expected, since the pharmacological mechanisms of action of the two drugs are different.

- In an animal physical dependence study, chronic administration of istradefylline did not produce signs of withdrawal during drug discontinuation. This suggests that istradefylline does not produce physical dependence.

- In a human abuse potential (HAP) study, oral administration of istradefylline at therapeutic (40 mg) and supratherapeutic (80 and 160 mg, 2-4X) doses produced responses on positive subjective measures such as Drug Liking, Overall Drug Liking, and Good Drug Effects that were within the acceptable placebo range. This suggests that istradefylline does not produce rewarding effects.

- Euphoria and other abuse-related adverse events (AEs) were not reported at a rate greater than placebo in Phase 1 or Phase 2/3 clinical studies following acute or chronic administration of istradefylline. This demonstrates that istradefylline does not produce positive effects that are supportive of abuse potential.

- Following discontinuation of istradefylline in Phase 2/3 clinical studies, there were no AEs indicative of withdrawal during the 40-day drug discontinuation phase. This suggests that istradefylline does not induce physical dependence.

III. RECOMMENDATIONS

Based on the CSS determinations that istradefylline has negligible abuse potential, will have a currently accepted medical use upon NDA approval, and does not appear to produce physical dependence, CSS concludes that:

a) Section 9 (Drug Abuse and Dependence) may be deleted from the drug label, as proposed by the Sponsor.

b) Istradefylline should not be recommended for control under the Controlled Substances Act.

IV. DISCUSSION

A. Chemistry

1. Drug Substance

Istradefylline (USAN name) is a new molecular entity identified by CAS registry number: 155270-99-8. It is chemically known as (*E*)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione. It has a molecular formula of $C_{20}H_{24}N_4O_4$ and a molecular weight of 384.429 g/mol. It is freely soluble in chloroform, slightly soluble in acetonitrile, sparingly soluble in dimethyl sulfoxide and dimethyl formamide

2. Drug Product

The drug product is formulated in two strengths, 20 and 40 mg, in a peach-colored, pillow-shaped, film-coated tablet. The formulation contains the following inactive ingredients: microcrystalline cellulose, crospovidone, polyvinyl alcohol, magnesium stearate (b) (4).

B. Preclinical Abuse-Related Studies with Istradefylline

1. Receptor Binding and Functional Studies

a. Receptor Binding Studies with Istradefylline (Study # AL-2189-G-r-en, AL-2189-r-en, 96-579-r-en, 6002-us-al-6796-r-en)

In human recombinant cells, istradefylline has high affinity for the adenosine A2A (Ki = 12 nmol/L) and A2B (Ki = 150 nmol/L) receptors, but no significant affinity for adenosine A1 or A3 receptors (Ki > 1000 nmol/L).

When istradefylline evaluated in a receptor binding test at abuse-related receptors, it was found to be inactive (defined as <50% inhibition at concentrations up to 10 μmol/L) at the following sites: Cannabinoid CB1 *and* CB2; Acetylcholine nicotinic; Dopamine (D1,

2, 3, 4, 5); Opioid (mu, kappa, delta); Sigma; GABA (A, B, transporter, benzodiazepine); Serotonin (1A, 1B, 1D, 2A, 2B, 2C, 3, 5A, 6, 7, and transporter); Glutamate (NMDA, phencyclidine, polyamine, glycine, kainate); norepinephrine (transporter).

Thus, istradefylline is a highly-selective adenosine A2a and A2b ligand.

b. Functional Study with Istradefylline (Study # d-06-189)

A functional study was conducted with rat pheochromocytoma PC-12 cells expressing A2A receptors to measure the effects of istradefylline on intracellular accumulation of cyclic adenosine monophosphate (cAMP) in response to application of CGS21680, an A2A agonist. If istradefylline has activity as an antagonist, it would block cAMP response to CGS21680.

Following application of CGS21680, cAMP accumulated in a concentration-dependent fashion. Subsequent application of istradefylline (1.5, 3 or 10 nmol/L) shifted the concentration-response curve of CGS21680 to the right. These data show that istradefylline has activity as an antagonist at adenosine A2A receptors. When istradefylline was administered alone, it had no effect on basal cAMP levels, confirming that it was a full antagonist at A2A receptors.

2. Animal Behavioral Studies

a. General Behavioral Observations

i. Mouse Irwin Test (Acute Oral Administration) (Study # 95-382, 95-382-r-en, KHK23-952834, 6002-m4213-02-khk23-952834-khk-23-esr)

In an Irwin study conducted in mice during a toxicity study, istradefylline was tested at oral doses of 0.1 to 300 mg/kg. The following behaviors were observed: doses >1 mg/kg: increased locomotor activity, touch response, grooming, and vocalization; ≥10 mg/kg: increase in respiration rate was observed; ≥30 mg/kg: locomotor activity, grooming and touch
response; ≥100 mg/kg: vocalization.

ii. Mouse Locomotor Studies (Study #95-382, 95-382-r-en)

In a locomotor study in mice, istradefylline was tested in oral doses of 0, 0.01, 0.04, 0.16, 0.63, 2.5, 10 mg/kg. At doses ≥0.16 mg/kg there was a dose-dependent increase in magnitude of locomotion as well as duration of activity. This effect was maximal at 2.5 mg/kg.

The data from these two studies show that istradefylline produces an increase in locomotor activity, which would be expected from a drug that has a mechanism of action similar to that of caffeine.

b. Abuse-Related Behavioral Studies

i. Drug Discrimination Study with Istradefylline (Study #6002-us-rs1393-r-en-esr)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug.

Method

Female rats (n = 6-10/group) were trained to discriminate amphetamine (0.5 mg/kg, i.p.) from vehicle. Amphetamine is a dopamine releaser that produces stimulant effects. During training, the schedule of reinforcement was gradually raised from fixed ratio (FR) 1 to FR5. Full generalization was defined as 75% accuracy on the drug-associated lever.

When intraperitoneal amphetamine discrimination was stable, animals were challenged with oral doses of amphetamine (0.25, 0.375, and 0.5 mg/kg, 15 minute pretreatment time), bupropion (10, 30, and 50 mg/kg, 30 minute pretreatment time), phentermine (1, 2, 3, 3.5, and 5 mg/kg, 15 minute pretreatment time) and istradefylline (10, 30, 90, and 120 mg/kg, 4 hour pretreatment time). Pharmacokinetic data from a separate group of rats shows that the doses of istradefylline produce plasma levels at Tmax (4 hours) that are (respectively) ~0.8X, 2X, 2.8X, and 4X the plasma levels produced in humans following a 40 mg dose of istradefylline.

Results

Full generalization to the intraperitoneal amphetamine cue was seen following administration of 0.5 mg/kg oral amphetamine (76%), 5 mg/kg oral phentermine (93%). Bupropion did not produce full generalization, even at the highest oral doses tested (30 mg/kg (60%) and 50 mg/kg (63%)). For istradefylline, the highest generalization to intraperitoneal amphetamine occurred at the 30 mg/kg oral dose (57%), equivalent to 2X the therapeutic dose, but this level of partial generalization does not suggest similarity to amphetamine.

Conclusions

This study shows that at therapeutic or supratherapeutic doses, istradefylline does not produce full generalization to the cue for amphetamine. This would be expected since these two drugs have non-overlapping mechanisms of action.

ii. Self-Administration Study in Rats with Istradefylline (Study #DG12184)

Methods

A self-administration study was conducted in male Rhesus monkeys (n = 4) to evaluate whether istradefylline produces sufficient reward to be reinforcing. Animals were trained to press a lever to receive cocaine (0.03 mg/kg/infusion, i.v.) using an FR5 schedule of reinforcement. After cocaine self-administration was stable for three sessions ((≥11 infusions/session with infusions limited to 20 infusions/day), animals were provided with saline to induce extinction. Challenge sessions with istradefylline were then started.

Istradefylline was tested at (0.125, 0.25 and 0.5 mg/kg/infusion) for 2 hours/day and 4 days/dose, using an FR5 schedule of reinforcement. The number of istradefylline infusions was limited to 20/day. The drug solution was formulated using a combination of istradefylline in N,N'-dimethylacetamide (DMAA), polyethylene glycol 400, and saline, because the drug is insoluble in saline alone. On the first day of each period, two consecutive, non-contingent infusions of the dosing formulations (cocaine, saline, istradefylline or vehicle) were administered. Forced administration did not occur if self-administration was observed at least twice prior to the first forced administration. The number of self-administrations was calculated by subtracting the number of forced administrations.

During CSS review of the preliminary report for this study in 2014, CSS requested additional information regarding the pharmacokinetics of istradefylline in monkeys in order to evaluate the doses used. We received the following information:

> "The estimated istradefylline concentration in plasma at time 0 after administration (C0), the elimination half life (t1/2) and the area under the plasma concentration-time curve from zero to infinity (AUC0-∞) were studied in rhesus monkeys after a single intravenous administration at doses of 0.25 and 0.5 mg/kg. The C0 value for the 0.25 mg/kg dose was 246 ng/ml, and for the for the 0.50 mg/kg dose was 355 ng/ml. Since the 0.125 mg/kg dose was not tested in the PK study, the Sponsor calculated an estimation of the value by halving the 0.25 mg/kg value of C0.
>
> "Based on data submitted by the Sponsor, administration of istradefylline at the proposed clinical dose of 20 mg/day for 14 days in patients with Parkinson's disease produces a Cmax value of 234 ng/ml in elderly males and 255 ng/ml in elderly females. The Sponsor asserts that these Cmax values are equivalent to the C0 values produced in animals using the 0.25 mg/kg self-administration dose.

> "The middle dose of istradefylline for the self-administration study was set at 0.25 mg/kg, which was expected to produce exposure to istradefylline similar to that produced by the proposed lower clinical dose of 20 mg/day (Cmax 234-255 ng/mL). The high dose for self-administration was 0.5 mg/kg of istradefylline, which is twice the middle dose (and twice the exposure produced by the clinical dose of 20 mg/day). The low dose for self-administration was 0.125 mg/kg of istradefylline, which is half the middle dose (and half the exposure produced by the 20 mg/day clinical dose)."

Results

The results show that all 4 monkeys self-administered the maximum infusions of cocaine (n = 20 infusions) while there was a low degree of self-administration of saline (n = 0.7 to 7.0 infusions) and vehicle (n = 0.7 to 6.0 infusions). Self-administration of istradefylline for each of the 4 monkeys was also low for each dose: 0.125 mg/kg/ infusion (n = 0.3, 7.7, 9.7, and 10.7 infusions), 0.25 mg/kg/infusion (n = 0, 0.3, 9.3, and 10.3 infusions), 0.5 mg/kg/ infusion (0, 0, 1, and 6 infusions).

Conclusions

These data appear to suggest that istradefylline was self-administered at rates that are similar to those produced by saline or vehicle, and are half that produced by cocaine. However, on August 19, 2014, CSS reviewed a preliminary report for this study and informed the Sponsor that:

"The self-administration study with istradefylline is not valid for two reasons:

"1) The doses selected for the self-administration study are inappropriate to evaluate the rewarding properties of istradefylline. The information you provided shows that the middle dose of istradefylline that was selected for the self-administration study produces plasma levels that are equivalent to those produced by the human therapeutic dose. However, doses for self-administration studies are typically fractions of the human exposure, so that animals bar-press to receive multiple infusions of the drug as a demonstration of the drug's reinforcing properties. Thus, if a single self-administration infusion produces plasma levels of the drug that are sufficiently rewarding to an animal, there will be a low level of continued bar-pressing. Such data can be misinterpreted as showing the drug has no abuse potential, when the drug actually produces rewarding responses.

"2) Given that the 5% DMAA vehicle solution produces adverse behavioral effects (and the death of 2 monkeys), it is not possible to determine whether the lack of self-administration in animals was due to a lack of rewarding effects or due to adverse physical effects from the DMAA solution. Although you conclude in the current study report that exposure to 5% DMAA for less than 4 days does not produce physical decline, the self-administration study was conducted for longer than 4 days. Thus, we agree with your previous statement that this solution can induce "deterioration of the physical

condition." Therefore, use of the 5% DMAA solution in a self-administration study is inappropriate. Since it is not possible to adequately solubilize istradefylline in any solution other than 5% DMAA for intravenous administration, it appears that an appropriately-designed self-administration study with istradefylline is not viable."

Thus, the self-administration study is not valid for the evaluation of whether istradefylline produces rewarding properties.

3. Physical Dependence Studies in Animals

Rat Physical Dependence Study with Istradefylline (Study # RS1394)

Methods

A rat physical dependence study was conducted in which rats (n = 10/group) received twice daily oral doses of istradefylline (10 or 60 mg/kg = 20 or 120 mg/kg/day), morphine (30 mg/kg = 60 mg/kg/day), or vehicle over a 28-day period. The Sponsor states that the doses of the istradefylline were selected to ensure plasma exposure in rats that is >3X the human AUC at the intended clinical dose (AUC_{0-24} = 9831 ng/ml*hr), based on a previously-conducted pharmacokinetic study. In a parallel pharmacokinetic study conducted during this physical dependence study, the 10 mg dose of istradefylline produced 1.1 to 1.6X the human C_{max} while the 60 mg/kg dose produced 4.9 to 6.0X the human C_{max}.

Rats were evaluated for withdrawal signs for 7 days after final drug administration. This duration is appropriate, since the half-life of istradefylline in rats is 2-6 hours. Evaluation during the drug discontinuation period occurred by monitoring food and water intake (twice daily), body weight (once daily), and temperature (twice daily), and changes in behavior (twice daily), using a checklist that included the following:

- Sedation
- Ataxia / rolling gait
- Drooping abdomen
- Abnormal posture (leaning to one side)
- Hunched posture (sitting or walking)
- Subdued
- Head weaving
- Straub tail
- Prostration
- Rearing
- Jumping
- Escape attempts from the cage
- Head shakes
- Body tone
- Locomotor activity

- Stereotypy
- Vacuous chewing movements
- Writhing
- Tremors
- Seizures
- Irritability on dosing / gentle restraint
- Aggression (pen inserted into cage)
- Cowering/hiding
- Vocalization (spontaneous)
- Piloerection
- Eye twitch
- Erratic respiration
- Respiration
- Salivation
- Teeth chattering
- Stained fur
- Stained eyes
- Eye discharge
- Stained nose
- Darkened hind limbs
- Diarrhea

Results

Abrupt discontinuation of vehicle after the 28-day dosing period produced no behavioral signs in at least 5 of 9 rats during the 7-day drug discontinuation phase. There were 1-2 rats that occasionally exhibited irritability or increased locomotor activity, but these behaviors were not observed consistently across the discontinuation period.

Abrupt termination of morphine after the 28-day dosing period produced behavioral signs of physical dependence. During the 7-day drug discontinuation phase, the following signs were observed in at least 5 of 10 morphine-treated rats: hunched posture, subdued behavior, increased locomotion, Straub tail, irritability, and piloerection. These behaviors are consistent with an opioid withdrawal syndrome, which validates the study.

Abrupt termination of istradefylline dosing (at either 10 mg/kg, bid, or 60 mg/kg, bid) produced no behavioral signs in at least 5 of 10 istradefylline-treated rats. There were 1-2 rats that occasionally exhibited irritability or increased locomotor activity, but these behaviors were not observed consistently across the discontinuation period.

Conclusions

Istradefylline did not produce signs of withdrawal during drug discontinuation following chronic administration. This suggests that istradefylline does not produce physical dependence.

C. Animal and Human Pharmacokinetics of Istradefylline

Table 1 (below) shows the pharmacokinetic profile following oral administration of istradefylline to rats and humans with regard to maximum plasma levels (Tmax), maximum plasma levels (Cmax) and half-life ($t_{1/2}$).

Table 1: Pharmacokinetic Parameters in Rats and Humans Following Acute Oral Administration

Species	Tmax (hr)	Cmax (ng/ml)	t½ (hr)
Rat (10 mg/kg)	2-3	60	2-6
Human (40 mg)	3	178.5	69 to 148 (2.9 to 6.1 days)

In humans, 40 mg oral istradefylline produces a Cmax of 178.5 ng/ml, with a median time to maximal plasma concentration (Tmax) of 3 hours (range 2-5 hours). The 40 mg dose of istradefylline produces a median half-life of ~69 hours (2.9 days).

The principal metabolite of istradefylline is M1 (4'-*O*-demethyl istradefylline), but exposure is extremely low: 1-3% of the exposure to the parent, istradefylline. Therefore, it is unlikely to that M1 contributes to the pharmacologic effects of istradefylline.

D. Clinical Abuse-Related Studies with Istradefylline

1. Human Abuse Potential Study: A Double-Blind, Randomized, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Istradefylline in Recreational Drug Users (Study #6002-017)

This was a randomized, double-blind, placebo-controlled, 6-way crossover study that evaluated the oral abuse potential, safety, and tolerability of istradefylline compared to placebo and phentermine in healthy nondependent recreational stimulant users. The study consisted of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

Subjects

Subjects

Subjects were healthy male and female adults, between 18 and 55 years of age, inclusive, who were non-dependent, non-treatment seeking recreational stimulant users. Of the 94 subjects who participated in the Qualification Phase, 55 entered the Treatment Phase, with a total of 42 study completers.

Inclusion Criteria for participation are standard but included the following criteria that are relevant for a human abuse potential study:

- The subject had a history of at least 10 lifetime non-therapeutic experiences (i.e., for psychoactive effects) with stimulants (e.g., amphetamine, cocaine, methamphetamine, methylphenidate, MDMA, phentermine, but not including nicotine or caffeine).

- The subject had at least 1 non-therapeutic experience with stimulants in the prior year.

Exclusion Criteria are standard but included the following criteria that are relevant for a human abuse potential study:

- Alcohol or substance dependence within the 12 months prior to Screening (except nicotine) including cannabis, as defined by the DSM-IV-TR, or any self-reported dependence or "addiction" within the subject's lifetime (with the exception of nicotine).

- Subjects who had ever been in treatment for substance use disorder(s) (except smoking cessation) or who are currently seeking treatment for substance use disorder(s).

- Subjects who tested positive on urine drug screen (UDS) or breath alcohol test.

Main Study:

The Main Study consisted of a Qualification Phase and a Treatment Phase. Subjects passed the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- Peak scores in response to 60 mg phentermine greater than that of placebo on Drug Liking visual analog scale (VAS) (difference of at least 15 points) with a minimum peak score of 65 points, and acceptable overall responses to phentermine and placebo on the subjective measures, as judged by the investigator or designee.

- Acceptable placebo response based on Drug Liking VAS (score between 40 and 60 points, inclusive).

- Subject was able to tolerate 60 mg phentermine, as judged by the investigator.

- General behavior suggestive that the subject could successfully complete the study, as judged by the clinic staff.

Subjects were required to fast (abstain from food) from at least 8 hours prior to and

until at least 4 hours after study drug administration in the Qualification and Treatment Phases. The Tmax of istradefylline occurs 2-5 hours after drug administration, so serving food at 4 hours is acceptable.

Given the similarity in mechanism of action between istradefylline and caffeine, subjects were not permitted to consume caffeine or xanthine-containing food or beverages from at least 12 hours prior to until at least 24 hours after each drug administration.

Subjects were required to abstain from smoking or use of nicotine replacement therapy for at least 2 hours prior to each study drug administration. Smoking or use of nicotine replacement therapy were permitted at short breaks (approximately 10 minutes in duration) after the 8-hour post-dose procedures.

Oral Drug Doses

Main Study

Qualification Phase (single blinded)

The following treatments were administered orally:

- 60 mg phentermine
- placebo

The 60 mg phentermine is intermediate to the two doses administered in the Treatment Phase (45 and 90 mg).

There was a washout period of at least 48 hours in between treatments. At the conclusion of the Qualification Phase, there was a 96 hour (4 day) washout period before initiation of the Treatment Phase.

Treatment Phase (double-blind)

The following treatments were administered orally:

- Istradefylline 40 mg
- Istradefylline 80 mg
- Istradefylline 160 mg
- Phentermine 45 mg
- Phentermine 90 mg
- Placebo

At the time the HAP study was conducted, 40 mg of istradefylline was considered to be a "potential therapeutic dose." In the present NDA submission, the Sponsor states that the starting therapeutic dose is 20 mg/day, with a potential increase to 40 mg/day if the lower

dose does not produce sufficient therapeutic benefit. Thus, the 40 mg dose in the HAP study represents the high therapeutic dose, while the 80 and 160 mg doses are 2X and 4X the 40 mg dose. At the time the HAP study was designed, the Sponsor stated that the 160 mg dose of istradefylline was expected to be safe and tolerable because doses between 100 mg and 200 mg istradefylline were well-tolerated in a single ascending dose study. Higher doses (300 mg and greater) were not considered acceptable because of known aversive AEs such as nausea, vomiting, and headache.

The doses of phentermine (45 mg to 90 mg) have been used in published human abuse potential studies.

There was a washout period of at least 21 days between treatments, based on a half-life of istradefylline in Phase 1 studies of 69 hours after acute administration.

Pharmacodynamic Variables

All subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration, except for VAS for Overall Drug Liking, Take Drug Again, which were assessed at 12 and 24 hours. The Caffeine Withdrawal Symptom Questionnaire (CWSQ) was assessed at baseline and at 24 hours.

Primary Measure:

Drug Liking VAS (bipolar)

Secondary Measures:

Balance of effects:
- Overall Drug Liking VAS (bipolar)
- Take Drug Again VAS (unipolar)

Positive and negative effects:
- Good Effects VAS (unipolar)
- Bad Effects VAS (unipolar)

Stimulation effects:
- Alertness/Drowsiness VAS (bipolar)
- Agitation/Relaxation VAS (bipolar)

Other drug effects:
- Any Effects VAS (unipolar)
- Drug Similarity VAS

In addition to the VAS above, the Caffeine Withdrawal Symptom Questionnaire (CWSQ) was used. The CWSQ consists of 23 items developed based on caffeine withdrawal symptoms that were identified in a comprehensive review of prior research, including the

following categories of response: Fatigue/drowsiness; Low alertness/ Difficulty concentrating; Mood disturbances; Low sociability/ Motivation to work; Flu-like feelings and Headache. Subjects are asked to rate each item in terms of how they are feeling at that moment on a 5-point scale from 0 (not at all) to 4 (extremely).

Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG
- Physical examination findings
- Columbia Suicide Severity Rating Scale (C-SSRS) examination
- Concomitant medication usage.

Pharmacokinetic Evaluation

During the Treatment Phase, blood samples were collected immediately before each study drug administration and 0.5, 1, and 3 hours after the start of each study drug administration to monitor the pharmacokinetics of each study treatment.

Results

The following analysis of the HAP study subjective measures presented below in quotations is the **verbatim** statement from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ran Bi ("the reviewer"), FDA Office of Biostatistics (April 23, 2019):

"For the primary analysis, the reviewer suggests using one-sided test for all comparisons: 15 as the margin for the studying validity, to be consistent with the value used in the Qualification Phase; 11 should be used as the margin for comparing between Istradefylline and Placebo, as recommended in Chen & Bonson, 2013. Since this study was conducted before 2017 *FDA Guidance for Industry: Assessment of Abuse Potential of Drugs* was published, it is OK to use 0 as the test value for the comparison between Phentermine and Placebo.

"To evaluate abuse potential of Istradefylline, the reviewer performed statistical analysis for the primary endpoint, Drug Liking Emax, for the following questions, with the tested hypotheses and contrasts defined as follows:

"1. Does the positive control (C-Phentermine) produce mean Drug Liking Emax that shows greater abuse potential compared to Placebo (P)?

$$H0: \mu C - \mu P \leq 15 \text{ vs. } Ha: \mu C - \mu P > 15$$

"This hypothesis is for the study validation. Test value of 15 was chosen in order to be consistent with the value used in the Qualification Phase. Hypothesis 1 was applied to the following contrasts:

- Ph45 versus P
- Ph90 versus P

"2. Does the test drug (T-Istradefylline) produce mean Drug Liking Emax that shows less abuse potential compared to positive control (C-Phentermine)?

$$H0{:}\mu C - \mu T \leq 0 \text{ vs. } Ha{:}\mu C - \mu T > 0$$

"This hypothesis is for investigation of the abuse potential of the test drug Istradefylline, compared to the positive control Phentermine. Test value of 0 was chosen same as sponsor did. Hypothesis 2 and was applied to the following contrasts:

- Ph45 versus Is40
- Ph45 versus Is80
- Ph45 versus Is160
- Ph90 versus Is40
- Ph90 versus Is80
- Ph90 versus Is160

"3. Does the test drug (T-Istradefylline) produce mean Drug Liking Emax that shows similar abuse potential compared to placebo (P)?

$$H0{:}\mu T - \mu P \geq 11 \text{ vs. } Ha{:}\mu T - \mu P < 11$$

"This hypothesis is to investigate whether the test drug Istradefylline had similar abuse potential compared to Placebo. Test value of 11 was chosen based on *Chen and Bonson (2013)*. Hypothesis 3 was applied to the following contrasts:

- Is40 versus P
- Is80 versus P
- Is160 versus P

"The reviewer's primary analysis was conducted on Drug Liking Emax. The means of maximum drug liking of both Phentermine 45 mg and 90 mg (72.0 and 79.1) were statistically significantly greater than that of Placebo (57.9) by 9.8 and 16.9 points, respectively. Since the study was conducted before 2017 FDA *Guidance for Industry: Assessment of Abuse Potential of Drugs* was published, the test value of this comparison was 0. Therefore, the results from this comparison demonstrated the validity of the study. The mean differences of maximum drug liking between both doses of Phentermine and each dose of Istradefylline were statistically greater than 4.0 to 13.0 points. The mean difference between each dose of Istradefylline and Placebo was statistically significantly less than 11 points.

"The reviewer's primary analysis showed that for Drug Liking Emax,

- The mean difference between Phentermine 90 mg and Placebo was statistically significantly greater than 15 points, confirming the study validity;
- The mean difference between Phentermine 45 mg and Placebo was statistically significantly greater than 9.8 points;
- The mean of each dose of Phentermine was statistically significantly greater than that of all doses of Istradefylline;

- The mean difference between each dose of Istradefylline and Placebo was statistically significantly less than 11 points.

"The reviewer did the secondary analysis for the Completer Population (N = 42), which showed that the mean of each dose of Phentermine was statistically significantly greater than that of Placebo. The mean of each dose of Phentermine was statistically significantly greater than that of all doses of Istradefylline, except the comparison between Phentermine 45 mg and Istradefylline 40 mg on Bad Drug Effects Emax, and comparison between Phentermine 45 mg and Istradefylline 160 mg on Overall Drug Liking Emax and Bad Drug Effects Emax at significance level 0.05. In addition, Overall Drug Liking Emax and Take Drug Again Emax of Istradefylline were significantly greater than Placebo except Istradefylline 40 mg, Good Drug Effects Emax of Istradefylline was significantly greater than Placebo except Istradefylline 80 mg.

"The results from the reviewer's secondary analysis showed that for Overall Drug Liking Emax, Take Drug Again Emax, Good Drug Effects Emax, and Bad Drug Effects Emax:

- The mean of each dose of Phentermine was statistically significantly greater than that of Placebo;
- The mean of each dose of Istradefylline was statistically significantly smaller than that of either dose of Phentermine except the comparison between Phentermine 45 mg and Istradefylline 40 mg on Bad Drug Effects Emax (p-value = 0.0551), and comparison between phentermine 45 mg and Istradefylline 160 mg on Overall Drug Liking Emax and Bad Drug effects Emax (p-value = 0.0607 and 0.1808, respectively) at significance level 0.05;
- Istradefylline 40 mg had statistically significantly larger mean than Placebo on Good Drug effects Emax (p-value = 0.0009), but not significantly differentiated from Placebo on Overall Drug Liking Emax, Take Drug Again Emax, and Bad Drug Effects Emax;
- Istradefylline 80 mg had statistically significantly larger mean than Placebo on Overall Drug Liking Emax and Take Drug Again Emax (p-value = 0.0059 and 0.0241, respectively), but not significantly differentiated from Placebo on Good Drug Effects Emax and Bad Drug Effects Emax;
- Istradefylline 160 mg had statistically significantly larger mean than Placebo on Overall Drug Liking Emax, Take Drug Again Emax, and Good Drug Effects Emax (p-value = 0.0140, 0.0135 and 0.0336, respectively)."

Table 3 (below) depicts the effects of study treatments on subjective measures used in this study. The mean and standard deviation numbers provided below were drawn from the statistical review performed by Dr. Ran Bi.

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an acceptable placebo range of 40-60. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20.

Study Validation

As shown in Table 2 (below), the positive control drug, phentermine (45 and 90 mg), produced expected increases in positive subjective responses on the primary measure of Drug Liking (72 and 79 out of 100, respectively), that were outside the acceptable placebo range (40-60 out of 100 on a bipolar scale) and were statistically significantly greater than those produced by placebo. This validates the study.

Table 2: Effects of Oral Placebo, Phentermine (45 and 60 mg), and Istradefylline (40, 80, and 160 mg) on Key Subjective Measures (VAS) – E_{max} Scores (scale 0-100, mean and standard deviation) (n = 42)

	Placebo	PHENT 45 mg	PHENT 90 mg		ISTRA 40 mg	ISTRA 80 mg	ISTRA 160 mg
Drug Liking (bipolar)	58 ± 12	72 ± 15 *	79 ± 16 *		62 ± 12 ^ ~	63 ± 13 * ^ ~	62 ± 13 * ^ ~
Overall Drug Liking (bipolar)	52 ± 17	63 ± 20 *	71 ± 24 *		56 ± 18 * ^	60 ± 15 * ^	59 ± 12 * ^
Good Drug Effects (unipolar)	15 ± 23	45 ± 31 *	56 ± 28 *		24 ± 22 * ^	26 ± 27 * ^	26 ± 28 * ^
Take Drug Again (unipolar)	21 ± 30	48 ± 33 *	60 ± 33 *		28 ± 30 * ^	36 ± 35 * ^	33 ± 34 * ^
Bad Drug Effects (unipolar)	4 ± 9	15 ± 25	21 ± 26		7 ± 15 *	5 ± 14 *	7 ± 12 *

PHENT = phentermine, ISTRA = istradefylline
* = $p < 0.01$ compared to placebo, ^ = $p < 0.01$ compared to phentermine 45,
~ = $p < 0.01$ compared to phentermine 90

Drug Liking and Overall Drug Liking

- On the Drug Liking primary measure, istradefylline at 80 and 160 mg produced an increase in response that was statistically significantly greater than placebo (62-63 vs. 58 out of 100, respectively). However, both of these istradefylline responses were barely outside of the acceptable placebo range (40-60 out of 100 for bipolar scale).

- On the Overall Drug Liking measure, all three istradefylline doses produced statistically significant increases on this measure compared to placebo (56-60 vs. 52 out of 100, respectively), but none of these responses were outside of the acceptable placebo range (40-60 out of 100 for a bipolar scale). In contrast, phentermine at the highest dose (90 mg) did produce Overall Drug Liking that

was outside the placebo range and was also statistically significantly different from placebo (71 vs. 52 out of 100, respectively). For each dose of istradefylline on these measures, the responses were statistically less than that of phentermine.

Good Drug Effects, Take Drug Again, and Bad Drug Effects

- For Good Drug Effects, istradefylline at each dose produced a response that was statistically significantly greater than placebo (24-26 vs. 15 out of 100), but was barely outside of the acceptable placebo range (0-20 for unipolar scale). In comparison, phentermine at both doses produced a statistically significantly greater response (45 and 56 out of 100) than both istradefylline and placebo.

- For Take Drug Again, istradefylline at each dose produced a response that was statistically significantly greater than placebo (28-36 vs. 21 out of 100). This suggests that subjects would take istradefylline again, even though its ability to produce drug liking or good drug effects were marginal. In comparison, phentermine at both doses produced a statistically significantly greater response (48 and 60 out of 100) than both istradefylline and placebo.

- For Bad Drug Effects, all three doses of istradefylline produced an increase in response that was within the acceptable placebo range (0-20 for unipolar scales), even though they each were statistically significantly greater than placebo (5-7 vs. 4 out of 100). Although the responses from phentermine at both doses produced a statistically significantly greater response (15 and 21 out of 100) than both istradefylline and placebo, they were inside or barely outside the acceptable placebo range.

Table 3 (below) shows the results of subjective measures that were statistically evaluated by the Sponsor and not by the Office of Biostatistics. These include Alert/Drowsy VAS, Agitated/Relaxed VAS, and Any Drug Effect VAS. The Sponsor only provided mean values for each of these measures, but no information was provided about variation around the mean (e.g., standard deviation or standard error).

- For Alert/Drowsy and for Agitated/Relaxed VAS scales, istradefylline at all three doses produced an increase in response that was statistically significantly greater than placebo, but was either inside or barely outside of the acceptable placebo range (40-60 out of 100 for a bipolar scale). In contrast, phentermine at both doses produced an increase in response that was statistically significantly greater than placebo. However, for Agitated/Relaxed, this response was barely outside of the acceptable placebo range.

- For Any Drug Effect VAS, istradefylline at all three doses produced an increase in response that was statistically significantly greater than placebo. Phentermine at both doses produced a much larger increase in response that was statistically significantly greater than placebo and statistically significantly lower than any dose of istradefylline.

Table 3: Effects of Oral Placebo, Phentermine (45 and 60 mg), and Istradefylline (40, 80, and 160 mg) on Other Subjective Measures (VAS) – E_{max} Scores (scale 0-100, mean) (n = 42)

	Placebo	PHENT 45 mg	PHENT 90 mg		ISTRA 40 mg	ISTRA 80 mg	ISTRA 160 mg
Alert/Drowsy (bipolar)	55	72 *	79 *		62 * ^ ~	64 * ^ ~	61 * ^ ~
Agitated/ Relaxed (bipolar)	52	58 *	64 *		55 * ^ ~	55 * ^ ~	55 * ^ ~
Any Drug Effects (unipolar)	15	48 *	60 *		30 * ^ ~	27 * ^ ~	28 * ^ ~

PHENT = phentermine, ISTRA = istradefylline
* = $p < 0.01$ compared to placebo, ^ = $p < 0.01$ compared to phentermine 45,
~ = $p < 0.01$ compared to phentermine 90

Adverse Events

The adverse event profile was evaluated in the safety population (n = 47-49) from the Treatment Phase.

Euphoria

When euphoria-related AEs were evaluated, only "euphoria" itself was reported. The positive control drug, phentermine 45 and 90 mg, produced a high incidence of euphoria (n = 3 (6%), and n = 7 (15%), respectively). Placebo produced no euphoria (0%). Istradefylline produced a euphoria response in 1 of 42 subjects (2%) at the 40 and 160 mg doses, while the 80 mg dose produced no reports of euphoria.

Hypervigilance

Phentermine produced a higher incidence of hypervigilance at the 45 mg dose (n = 5, 11%) than the 90 mg dose (n = 3, 6%). Both placebo and the 40 mg dose of istradefylline produced a 4% rate of hypervigilance (n = 2 each). The two higher doses of istradefylline (80 and 160 mg) both produced a 6% incidence of hypervigilance (n = 3 each). It is likely that hypervigilance connotes an increase in cognitive monitoring rather than a positive subjective effect.

Insomnia

Phentermine produced a high incidence of insomnia (n = 9, 19%) at the 90 mg dose, while the 45 mg dose produced no insomnia, similar to that of placebo. Istradefylline at

40 mg produced no insomnia, while there were 1 (2%) and 2 (4%) subjects who reported insomnia at 80 and 160 mg, respectively.

Anxiety

Anxiety was seen at a low rate following each treatment: n = 2-3 (4-6%) for phentermine 45 and 90 (respectively), n = 0-2 (0-4%) for istradefylline 40, 80, and 160 mg, and n =1 (2%) for placebo.

Headache

Phentermine produced a high incidence of headache (n = 5, 10%) at both the 45 and 90 mg doses. In contrast, istradefylline produced a low incidence of headache (n = 1-2, 2-4%) for each of the three doses. This was slightly lower than the incidence produced by placebo (n = 3, 6%).

Thus, there do not appear to be meaningful abuse-related signals from the AE profile following administration of istradefylline.

Drug Similarity

On the Drug Similarity question (on scale of 0-100):

- The positive control, phentermine (45 and 90 mg), was identified as amphetamine (36 and 59, respectively)
- Placebo was identified as placebo (88)
- Istradefylline (40, 80, and 120 mg) was not identified as any drug (rating of < 5 out of 100)

This measure shows that although istradefylline has a mechanism of action similar to that of caffeine and produces clinical efficacy through its ability to increase wakefulness, it was not identified as caffeine or other stimulants. This suggests that istradefylline does not produce stimulant-like responses. Istradefylline was also not identified as placebo, opioid, THC, or LSD. This suggests that it does not have abuse potential.

Caffeine Withdrawal Symptom Questionnaire (CWSQ)

There were no differences in the mean CWSQ scores between any of the study treatments (placebo, phentermine, or istradefylline) at either the predose and 24 hours postdose assessments.

Columbia-Suicide Severity Rating Scale (C-SSRS)

No subjects who participated in the Treatment Phase had a change from baseline on the C-SSRS at any timepoint in the study or at follow-up.

Overall Conclusions

Phentermine at both doses (45 and 90 mg) produced expected positive subjective responses (Drug Liking, Overall Drug Liking, Good Effects, and Take Drug Again) that were statistically significantly greater than placebo. This validates the study.

Istradefylline at the doses tested (40, 80, and 160 mg) produced statistically significant increases on the four positive subjective measures, on the single negative measure (Bad Drug Effects), and also produced increases in VAS for Alert/Drowsy, Agitated/Relaxed, and Any Drug Effect compared to placebo. However, none of these responses to istradefylline were outside of the acceptable placebo range except for the responses on Take Drug Again. Given that istradefylline has a mechanism of action similar to that of caffeine, this response is unlikely to indicate that the drug has abuse potential, in the absence of other meaningful clinical abuse signals.

Additional support for the lack of abuse potential with istradefylline is seen in the absence of abuse-related AEs (including no pattern of euphoria). Similarly, in a Drug Similarity test, istradefylline was not identified as any drug of abuse.

These data support the conclusion that istradefylline does not have abuse potential.

2. Abuse-Related Adverse Events in Clinical Studies

a. Phase 1 Studies

To identify potential safety signals in the Phase 1 database, the safety data from 9 single-dose studies and 7 multiple-dose studies were evaluated. Doses of istradefylline tested in healthy individuals in these studies ranged from 10-400 mg/day. The safety database consisted of 2 pools of studies organized by extent of drug exposure:

Pool A: Single dose istradefylline exposure trials (6002-US-010, 6002-US-022, 6002-US-023, 6002-EU01, 6002-EU03, 6002-0205, 6002-9601, 6002-011, 6002-012)

Pool B: Multiple dose istradefylline exposure trials (6002-US-002, 6002-US-024, 6002-EU02, 6002-EU06, 6002-0104, 6002-9703, and PP15710)

None of the subjects in these Phase 1 studies experienced abuse-related AEs at a rate greater than 2%. None of the subjects reported a euphoria-related AE. The AEs that were reported included “floating feeling,” “sleep disorder,” and “feeling abnormal.” This pattern was observed for both single-dose and multiple-dose Phase 1 studies with istradefylline. Other prominent central nervous system (CNS) AEs included “headache” and “dizziness,” but these are not associated with abuse potential.

These data show that in healthy individuals, istradefylline does not produce euphoria or other AEs indicative of abuse potential.

b. Phase 2/3 Studies

To identify potential safety signals in the Phase 2/3 database, studies were evaluated in which istradefylline was administered as adjunctive therapy to levodopa/carbidopa or levodopa/benserazide in subjects with Parkinson's disease who were experiencing motor response fluctuations. These studies were double-blind, placebo-controlled, fixed-dose investigations that tested istradefylline at 10-60 mg/day. Most subjects were receiving standard anti-Parkinson treatment in addition to study drug and levodopa, so the "placebo" group represents the presence of these drugs without istradefylline.

Table 4: Treatment-emergent Adverse Events Reported for ≥ 2% of Subjects in the Total Istradefylline Group by Preferred Term

	Placebo N=1010 n (%)	Istradefylline				
		10 mg/day N=153 n (%)	20 mg/day N=869 n (%)	40 mg/day N=896 n (%)	60 mg/day N=155 n (%)	Total N=2073 n (%)
Hallucination	18 (1.8)	2 (1.3)	18 (2.1)	26 (2.9)	9 (5.8)	55 (2.7)
Somnolence	32 (3.2)	5 (3.3)	28 (3.2)	17 (1.9)	4 (2.6)	54 (2.6)
Fatigue	19 (1.9)	6 (3.9)	18 (2.1)	20 (2.2)	4 (2.6)	48 (2.3)
Insomnia	42 (4.2)	10 (6.5)	31 (3.6)	48 (5.4)	5 (3.2)	94 (4.5)
Anxiety	20 (2.0)	5 (3.3)	16 (1.8)	22 (2.5)	6 (3.9)	49 (2.4)
Headache	30 (3.0)	7 (4.6)	24 (2.8)	31 (3.5)	8 (5.2)	70 (3.4)
Dizziness	42 (4.2)	8 (5.2)	44 (5.1)	44 (4.9)	22 (14.2)	118 (5.7)
Nausea	46 (4.6)	11 (7.2)	52 (6.0)	54 (6.0)	35 (22.6)	152 (7.3)

Table 4 (above) shows the treatment-emergent AEs reported in Phase 2/3 studies with istradefylline. None of the subjects reported euphoria-related AEs during administration of istradefylline. "Hallucination" was reported at a rate of ~2-3% at the therapeutic doses (20-40 mg/day), similar to that of placebo (2%). The rate for "hallucination" was higher (~6%) at the supratherapeutic dose of 60 mg/day. "Somnolence" and "fatigue" were reported in 2-4% of patients across the administered doses, similar to that of placebo (2-3%). "Insomnia" was reported in 3-7% of patients across all doses, similar to that of placebo (4%). "Dizziness" was similar to that of placebo (4-5%) at all doses except for 60 mg/day (14%). "Headache" was similar for all doses and for placebo (3-5%). "Nausea" was reported in all doses at a rate similar to placebo (~5-7%), except for the 60 mg/day dose (23%).

These data show that in patients who participated in Phase 2/3 studies, istradefylline does not produce euphoria or other AEs indicative of abuse potential

3. Assessment of Human Physical Dependence (Study #6002-US-005, 6002-US-006, 6002-US-013, 6002-US-018, 6002-EU-007, 6002-009, 6002-0608 and 6002-014)

The Sponsor did not conduct a clinical study to evaluate the ability of istradefylline to produce physical dependence in humans.

However, in assessing the ability of istradefylline to produce physical dependence, it is important to consider the pharmacokinetics of the drug. The elimination half-life of istradefylline in humans following chronic administration ranges from 83 hours (3.4 days) to 148 hours (6 days). Since it takes 5 half-lives before a drug is fully eliminated from the body, it would take 15 to 30 days (2 to 4 weeks) before istradefylline was completely metabolized from a human. This very slow elimination period means that a rapid decrease in istradefylline plasma concentrations following an abrupt termination of dosing would not occur. Since a withdrawal syndrome is often associated with a rapid decrement in drug levels, it is unlikely that the slow elimination of istradefylline would produce a severe withdrawal syndrome.

In order to assess whether istradefylline discontinuation in clinical studies did produce signs of withdrawal, the Sponsor conducted an evaluation of adverse events for the 40 days following discontinuation of istradefylline in patients who participated in eight 12- or 16-week double-blind, placebo-controlled, randomized, Phase 2/3 studies. This 40-day period is greater than 5 elimination half-lives of istradefylline, and thus would adequately evaluate whether the drug produces AEs indicative of a withdrawal syndrome.

An assessment of the AEs during the drug discontinuation period show that there were no AEs for any organ system that were observed at a rate greater than 0.4% for either istradefylline (n = 2073) or placebo (n = 1010). This suggests that istradefylline does not produce meaningful signs of withdrawal indicative of physical dependence. This conclusion is consistent with the lack of withdrawal signs in the animal physical dependence study conducted with istradefylline.

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KATHERINE R BONSON
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Clinical Inspection Summary

Date	07/02/2019
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Stacy Metz, Regulatory Project Manager Leonard Kapcala, M.D., Medical Officer Natalie Branagan, M.D., Medical Officer Division of Neurology Products
NDA #	022075
Applicant	Kyowa Kirin, Inc.
Drug	Istradefylline
NME	Yes
Proposed Indication	Adjunctive treatment to devodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes
Consultation Request Date	3/21/2019
Summary Goal Date	6/28/2019, extended to 7/8/2019
Action Goal Date	8/27/2019
PDUFA Date	8/27/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Okamoto, Toda, and Yokochi were inspected in support of this NDA. These inspections covered Protocols 6002-0608 and 6002-009. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

This Clinical Inspection Summary is based on communications with the field investigator. Establishment Inspection Reports (EIRs) have not been received from the field and are pending final review. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

At one of the sites (Toda), the clinical investigator did not report a fall occurring in one subject since this subject had a medical history of a "propensity to fall" and the clinical investigator did not consider this event as a worsening of the propensity to fall. However, on face, it would be difficult to make such a determination. If the review division is interested in evaluating the overall occurrence of falls during this study, you may wish to consider asking the sponsor to provide this information.

II. BACKGROUND

Istradefylline oral tablets are being developed by Kyowa Kirin, Inc, under NDA 022075 (IND 058536), for the adjunctive treatment with levodopa/carbidopa in patients with Parkinson's Disease (PD) experiencing "OFF" episodes. Istradefylline was approved in Japan in 2013 for this indication.

Levodopa therapy has been associated with a "wearing-off" effect, in which PD symptoms are not controlled (OFF episodes). OFF episodes or OFF time refer to periods in which patients have greater difficulty with motor symptoms and includes issues with mobility, slowness, and stiffness. Levodopa therapy has also been associated with the development of dyskinesia as well as abnormal, uncontrolled, involuntary movements. Clinical trials evaluating the efficacy and safety of antiparkinsonian medications, including istradefylline, assess OFF time, ON time (when motor symptoms are controlled), and dyskinesias.

This NDA was originally submitted in 2007 and was not approved. During that review cycle, two US sites were inspected for two protocols (US-005, US-006). This NDA was resubmitted with additional efficacy and safety data from one Phase 2 trial (6002-0608) and one Phase 3 trial (6002-009), both conducted exclusively in Japan. The sponsor also submitted data from a Phase 3 trial (6002-014), conducted in US/nonUS clinical sites, which did not demonstrate efficacy.

The Pharmaceuticals and Medical Devices Agency (PMDA) conducted inspections of four clinical investigator sites enrolling in Protocols 6002-0608 and 6002-009 when the marketing application was under review in Japan (see summary of results in CIS). Clinical investigator inspections were conducted for Protocols 6002-0608 and 6002-009 as the sponsor considers them to be the pivotal trials supporting the efficacy of istradefylline in PD patients.

Protocol 6002-0608

Title: "Placebo-controlled, double-blind, parallel-group, fixed dose study of KW-6002 (istradefylline) in the treatment of Parkinson's Disease"

Subjects: 362 enrolled

Sites: 47 sites in Japan

Study Initiation and Completion Dates: 3/30/2007 to 8/5/2008

This was a randomized, placebo-controlled, double-blind study evaluating the efficacy and safety of istradefylline in subjects with Parkinson's Disease (PD) with motor complications on levodopa therapy.

The study included a Screening/Baseline Period (2 weeks) and a Double-Blind Period (12 weeks). During the Screening/Baseline period, subjects were trained on completion of ON/OFF subject diaries (source for primary efficacy endpoint). Subjects had to have at least

two hours of OFF time per day on at least 4 valid diaries completed during the 7-day period prior to randomization. Eligible subjects were randomized on Day -1 to one of three treatment groups:

- Istradefylline 20 mg/day
- Istradefylline 40 mg/day
- Placebo

Subject ON/OFF diaries were completed daily for the 7 days before each study visit. The *primary efficacy endpoint* was the change from baseline to last available post-baseline value in total hours of awake time per day spent in the OFF state, which was derived from the subjects' ON/OFF diaries.

Protocol 6002-6009

Title: "Placebo-controlled, double-blind, parallel-group, confirmatory comparative study of KW-6002 in the treatment of Parkinson's Disease"

Subjects: 373 enrolled

Sites: 44 sites in Japan

Study Initiation and Completion Dates: 7/21/2009 to 2/21/2011

The study design for this Phase 3 study was essentially the same as Protocol 6002-0608.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, and enrollment in multiple pivotal clinical studies.

III. RESULTS

1. **Koichi Okamoto, M.D.**
   Gunma University Hospital
   3-39-15 Showa-machi
   Maebashi-shi
   Gunma 371-0034
   Japan

At this site for Protocol 6002-0608 (Site #385010), 17 subjects were screened, 14 were enrolled, and 11 completed the study. Three subjects discontinued the study, two due to noncompliance and one due to an SAE. Subject (b) (6), randomized to istradefylline, discontinued due to the SAE spinal compression fracture. For Protocol 6002-009 (Site #GM), 13 subjects were screened, 13 were enrolled, and 12 subjects completed the study. Subject (b) (6), randomized to istradefylline, discontinued due to the SAE of myocardial infarction. Brief subject narratives for these SAEs are included in the NDA submission.

The clinical site staff informed the FDA field investigator that the originals of certain source documents and records had been destroyed. A sponsor representative attended the inspection

and clarified that the original intention of the clinical trials was for submission to the Japanese regulatory authority, PMDA. The Japanese GCP Ordinance states that records shall be retained until the day on which the test drug receives marketing approval or three years after the date of premature termination or completion of the clinical trial, whichever comes later. PMDA approved istradefylline in March 2013; therefore, clinical sites could begin destroying records in December 2011 for Protocol 6002-0608 and in August 2014 for Protocol 6002-009. According to the FDA field investigator, despite the fact that the sites destroyed certain original documents, all pertinent records were available as either scanned PDFs uploaded into the subjects' electronic medical record or as photocopies maintained by the sponsor, which were provided during the inspection.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, MMSE scores, and primary efficacy endpoint.

The primary efficacy endpoint was the change from baseline to the last available post-baseline value in total hours of awake time per day spent in the OFF state, which was derived from the subjects' ON/OFF diaries. Subjects completed diaries indicating their state (ON or OFF) at half hour increments for the 7 days prior to each study visit. At this site, photocopies of subject diaries were available for review. All subject ON/OFF diary data were verified against the data line listing provided by the sponsor, and no discrepancies were identified. There was no evidence of under-reporting of adverse events.

2. Kazuo Toda, M.D.
Toda Internal Medicine and Rehabilitation Clinic
4-5-1 Nishikigaoka,
Uozumi-cho
Akashi-shi,
Hyogo 674-0081
Japan

At this site for Protocol 6002-009 (Site #TR), 23 subjects were screened, 21 were enrolled, and 18 completed the study. Three subjects discontinued the study; one subject withdrew consent and two were discontinued due to SAEs. Subject (b) (6), randomized to istradefylline, discontinued due to the SAE of bile duct cancer, and Subject (b) (6), randomized to placebo, discontinued due to the SAE of unexplained death. Brief subject narratives for these SAEs are included in the NDA submission.

The clinical site maintained original study documents that were available for inspection. Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability,

inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, MMSE scores, and primary efficacy endpoint data.

The primary efficacy endpoint was the change from baseline to the last available post-baseline value in total hours of awake time per day spent in the OFF state, which was derived from the subjects' ON/OFF diaries. Subjects completed diaries indicating their state (ON or OFF) at half hour increments for the 7 days prior to each study visit. At this site, hardcopies of subject diaries were available for review. All subject ON/OFF diary data were verified against the data listings provided by the sponsor, and no discrepancies were identified.

However, there may have been under-reporting of adverse events. For example, the medical record prior to screening for Subject (b) (6), randomized to istradefylline, noted "a propensity to fall." This subject fell during the clinical trial, and the resulting bruise (verbatim term contusion of breast) was reported as an adverse event but the fall was not. The clinical investigator stated that he did not consider this event as a worsening of the propensity to fall; therefore, he did not report it as an AE.

Reviewer comment: For Subject (b) (6), a fall occurring during the study was not reported as an adverse event. The medical record prior to screening for this subject, randomized to istradefylline, noted "a propensity to fall." The clinical investigator stated that he did not report the fall as an adverse event because he did not consider this event as a worsening of the propensity to fall. However, on face, it would be difficult to make such a determination. If the review division is interested in evaluating the overall occurrence of falls during this study, you may wish to consider asking the sponsor to provide this information.

3. Masayuki Yokochi, M.D.
Tokyo Metropolitan Ebara Hospital
4-5-10 Higashi Yukigaya
Ohta-ku, Tokyo 145-0065
Japan

At this site for Protocol 6002-0608 (Site #0205Z010), 12 subjects were screened, all of whom were enrolled, and 11 subjects completed the study. Subject (b) (6), randomized to istradefylline, discontinued the study due to the adverse event of uveitis. For Protocol 6002-009 (Site #EB), 13 subjects were screened, 12 were enrolled, and 9 completed the study. Three subjects discontinued the study due to the following reasons: SAE (Subject (b) (6), "acute drug intoxication"), physician decision (n = 1), and withdrawal by subject (n = 1).

- A brief narrative of the SAE for Subject (b) (6) is included in the NDA but does not provide a detailed description of the event. Subject (b) (6), randomized to placebo, had ingested ~nine days' worth of medications for Parkinson's disease (medications not specified but reportedly not investigational product), wandered 5 kilometers, then ingested medication for insomnia (not specified). Family had difficulty waking the subject, which led to the subject being hospitalized for four days. The clinical investigator made the decision to discontinue the subject as compliance with

investigational product dosing could not be assured. A psychiatry consult was obtained with the determination that the event was not consistent with a suicide attempt. Of note, the discontinuation category for this event was "physician decision" and not adverse event.

- Subject (b) (6), randomized to istradefylline, was discontinued due to physician decision in that the subject required a prohibited medication, warfarin, for treatment of deep vein thrombosis (DVT). DVT was reported as an adverse event in the sponsor line listings.

The clinical site staff informed the FDA field investigator that the originals of certain source documents and records had been destroyed. A sponsor representative attended the inspection and clarified that the original intention of the clinical trials was for submission to the Japanese regulatory authority, PMDA. The Japanese GCP Ordinance states that records shall be retained until the day on which the test drug receives marketing approval or three years after the date of premature termination or completion of the clinical trial, whichever comes later. PMDA approved istradefylline in March 2013; therefore, clinical sites could begin destroying records in December 2011 for Protocol 6002-0608 and in August 2014 for Protocol 6002-009. According to the FDA field investigator, despite the fact that the sites destroyed certain original documents, all pertinent records were available as either scanned PDFs uploaded into the subjects' electronic medical record or as photocopies maintained by the sponsor, which were provided during the inspection.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, MMSE scores, and primary efficacy endpoint data.

The primary efficacy endpoint was the change from baseline to the last available post-baseline value in total hours of awake time per day spent in the OFF state, which was derived from the subjects' ON/OFF diaries. Subjects completed diaries indicating their state (ON or OFF) at half hour increments for the 7 days before each study visit. At this site, photocopies of subject diaries were available for review. All subject ON/OFF diary data were verified against the line listings provided by the sponsor, and no discrepancies were identified.

Under-reporting of adverse events occurred in one of twelve subjects enrolled in Protocol 6002-0608. Subject (b) (6), randomized to istradefylline, presented to the emergency room with nausea, headache, and nasopharyngitis. The clinical investigator considered the nausea and headache to be secondary to the nasopharyngitis and therefore did not report them separately. Approximately ten days later, this subject was diagnosed and treated for bronchitis, which was reported as an adverse event.

Reviewer comment: The clinical investigator reported nasopharyngitis as an adverse event but not the nausea and headache present at the same time, as he believed these symptoms to be secondary to the nasopharyngitis. While headache can be a related symptom, nausea is usually not. However, it is unlikely that the under-reporting of one adverse event, i.e. nausea, would affect the overall safety assessment of this investigational product.

Pharmaceuticals and Medical Devices Agency (PMDA) Inspection Results

Istradefylline was approved in Japan in 2013 for the adjunctive treatment with levodopa/carbidopa in patients with Parkinson's Disease (PD) experiencing "OFF" episodes. As part of the review of this marketing application, PMDA conducted an inspection of the sponsor, Kyowa Hakko Kirin Co., Ltd., and four clinical investigator sites.

The clinical investigator sites inspected for Protocols 6002-0608 and 6002-009 were:

- Sites 1618040/YN (Junji Yoshinaga)
- Sites 0206A010/AB (Takashi Abe)
- Sites 0207A010/AT (Tetsushi Atsumi)
- Sites 0207I0001/KS (Noriko Kawashima)

The only significant observations for the clinical investigator inspections was a lack of MMSE source documents for all subjects in both protocols at Site 0206A010/AB (Takashi Abe). Inspectional observations for the sponsor inspection included not notifying the clinical investigators of adverse events associated with the investigational drug within the required time period per Japanese GCP and inadequate monitoring regarding the lack of MMSE source documents at Site 0206A010/AB.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analyst/Yolanda Patague

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07/08/2019 09:37:17 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 3, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 022075
Product Name and Strength:	Nourianz (istradefylline) tablets, 20 mg and 40 mg
Applicant/Sponsor Name:	Kyowa Kirin, Inc.
FDA Received Date:	June 24, 2019
OSE RCM #:	2019-490-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, blister labels, and carton labeling received on June 24, 2019 for Nourianz. Division of Neurology Products (DNP) requested that we review the revised container labels, blister labels, and carton labeling for Nourianz (Appendix A) to determine they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective.

- The placeholder for the serial number that is required as part of the human-readable product identifier is missing from the container labels.
- The 'Il' in the established name, istradefylline, on the PDP appears to be bolded.

We provide recommendations to address these concerns in Section 3 below.

[a] Little, C. Label and Labeling Review for Nourianz (NDA 022075). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 05. RCM No.: 2019-490.

3 RECOMMENDATIONS FOR KYOWA KIRIN, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels
    a. As currently presented, the container labels do not include a placeholder for the serial number that is required as part of the human-readable product identifier. Add the placeholder for serial number to comply with the Drug Supply Chain Security Act (DSCSA).
    b. The 'll' in the established name, istradefylline, on the PDP appears to be bolded and overly prominent. To improve readability, revise the established name to ensure that the font presentation is consistent (i.e., un-bold the 'll' in the established name).

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BRIANA B RIDER
07/03/2019 02:38:26 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 5, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 022075
Product Name and Strength:	Nourianz (istradefylline) tablets, 20 mg and 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kyowa Kirin, Inc.
FDA Received Date:	February 27, 2019
OSE RCM #:	2019-490
DMEPA Safety Evaluator:	Colleen Little, PharmD
Acting DMEPA Team Leader:	Briana Rider, PharmD

1 REASON FOR REVIEW

As part of the approval process for Nourianz (istradefylline) tablets, the Division of Neurology Products (DNP) requested that we review the proposed Nourianz prescribing information (PI), patient information, container labels, blister labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 022075 for istradefylline tablets was submitted on March 29, 2007. Subsequently, a not approvable letter was issued to the Sponsor on February 25, 2008.[a]

On February 27, 2019, Kyowa Kirin, Inc. (Kyowa) submitted a Class 2 resubmission under NDA 022075 in response to the February 25, 2008 not approvable letter.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Table 2 below includes the identified medication error issues with the submitted container labels, blister labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

[a] Wheelous, T. Not Approvable Letter for istradefylline tablets (NDA 022075). 2008 FEB 25. Available in DARRTS via: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af801381a8&_afrRedirect=23309235346 8490

Table 2. Identified Issues and Recommendations for Kyowa Kirin, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels, Blister Labels, and Carton Labeling			
1.	The format for the expiration date is not defined on the container labels (90-count bottles) and the carton labeling. Additionally, the expiration date format indicated on the blister label (i.e., 12/00) is not consistent with our recommended format.	Clearly define the expiration date to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The finished dosage form (i.e., tablets) appears after the strength statement (i.e., "20 mg" and "40 mg").	The established name should include the finished dosage form.[b]	Relocate the finished dosage form to appear after the established name (e.g., Nourianz (istradefylline) tablets).
Container Labels and Carton Labeling			
1.	The "recommended dosage" statement does not appear the container labels and carton labeling.	The "recommended dosage" statement is required per 21 CFR 201.55.	Revise the statement (b) (4) (b) (4) (b) (4) to read "Recommended dosage: see prescribing information" or a similar statement.
Container Labels			

Table 2. Identified Issues and Recommendations for Kyowa Kirin, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The net quantity statement (i.e., "90 tablets") is located in close proximity to the strength statement (i.e., "20 mg" and "40 mg").	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.[b]	Relocate the net quantity statement away from the strength statement.
2.	The human-readable and machine-readable (2D data matrix barcode) product identifiers are omitted from the smallest saleable unit.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
3.	The location for lot number and expiration date has not been identified.	The lot number and expiration date are required per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively.	Ensure that the lot number and expiration date are present. Additionally, ensure the lot number is clearly differentiated from the expiration date.
Blister Labels			

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[c] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 2. Identified Issues and Recommendations for Kyowa Kirin, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The net quantity statement (b) (4) is more prominent than the strength statement (i.e., "20 mg" and "40 mg").	The net quantity statement should not compete in prominence with the strength statement.[b]	Revise the blister label to ensure the net quantity statement is less prominent than the strength statement.
Carton Labeling			
1.	The color scheme of the 20 mg strength (b) (4) and the established name font appear in the same (b) (4).	The use of the same (b) (4) color for the 20 mg strength color scheme and for the established name and strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.[b]	Revise the established name font color (b) (4) so that the established name appears in black font to ensure consistency throughout labels and labeling (i.e., container labels and blister labels).
Blister Labels and Carton Labeling			
1.	The blister labels and carton labeling do not clearly state that the designated strength is per tablet.	The product strength on the principal display panel and other panels of the blister labels and carton labeling should describe the milligram amount of drug per tablet so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card.[a]	Revise the product strength to clearly communicate the strength per tablet (e.g., 20 mg per tablet).
2.	The proposed (b) (4) packaging configuration is not listed in Section 16 How Supplied/Storage and Handling, of the prescribing information.	It is unclear if the (b) (4) packaging configuration is intended for commercial use or as a professional sample.	Clarify if the (b) (4) packaging configuration is intended for commercial use or as a professional sample.

5 CONCLUSION

Our evaluation of the proposed Nourianz prescribing information (PI) and patient information did not identify areas of vulnerability that may lead to medication errors. However, our evaluation of the proposed Nourianz container labels, blister labels, and carton labeling

identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Kyowa Kirin, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Nourianz that Kyowa Kirin, Inc. submitted on February 27, 2019.

Table 3. Relevant Product Information for Nourianz	
Initial Approval Date	N/A
Active Ingredient	istradefylline
Indication	Indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes
Route of Administration	Oral
Dosage Form	Tablets
Strength	20 mg, 40 mg
Dose and Frequency	20 mg administered orally once a day. If a sufficient therapeutic response is not achieved, the dose may be increased to 40 mg once daily. Initial dose titration is not required.
How Supplied	90-count bottles (b) (4)
Storage	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].
Container Closure	The bottle presentation consists of a (b) (4) high density polyethylene (HDPE) bottle, sealed with (b) (4) (b) (4) closure. (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 22, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, istradefylline and NDA 022075. Our search identified no previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Nourianz labels and labeling submitted by Kyowa Kirin, Inc. received on February 27, 2019.

- Container labels
- (b) (4)
- Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

(b) (4)

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 6, 2007

TO: Teresa Wheelous, Sr. Regulatory Management Officer
Gerald Podskalny, M.D., Medical Officer
Division of Neurology Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-075

SPONSOR: Kyowa Pharmaceutical, Inc.

DRUG: Istradefylline Tablets (KW-6002)

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Indicated as adjunctive therapy to Levodopa/Carbidopa for the treatment of (b) (4) Parkinson's disease (PD) (b) (4) (b) (4).

CONSULTATION REQUEST DATE: June 14, 2007

DIVISION ACTION GOAL DATE: January 14, 2008

PDUFA GOAL DATE: February 25, 2008

I. BACKGROUND

Istradefylline is a novel, selective, adenosine A_{2A} receptor antagonist developed for use as adjunctive therapy to levodopa and carbidopa in the treatment of Parkinson's disease. Clinical investigator inspections were conducted at two clinical sites (Drs. Struck and Silver) submitting

data in support of NDA 22-075. These sites were inspected due to enrollment of large numbers of study subjects. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of adverse events, and protection of subjects' rights, safety, and welfare.

The inspections covered studies performed under the following protocols:

- Protocol: # 6002-US-005 entitled "A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study of the Efficacy of 40 mg/day KW-6002 as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy"

- Protocol: # 6002-US-006 entitled "A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study of the Efficacy of Doses of 20 and 60 mg/day KW-6002 as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy"

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)	Inspection Date	EIR Received Date	Final Classification
Dr. Lynne Struck, Site #19 Iowa Health Physicians 1221 Pleasant Street, Suite 300 Des Moines, IA 50309	6002-US-005	7/30/07-8/1/07	8/27/07	NAI
Dr. Dee Silver, Site #74 Coastal Neurological Medical Group, Inc. 9850 Genesee Avenue, Suite 740 La Jolla, CA 92037	6002-US-006	8/27/07-9/4/07	9/19/07	VAI

Key to Classifications
NAI - No deviation from regulations. Data acceptable.
VAI - No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI - Response Requested = Deviation(s) from regulations.
OAI - Significant deviations from regulations. Data unreliable.

(1) Dr. Lynne Struck, Site #19 Des Moines, IA

a. What was inspected?

Twenty-six subjects (26) were screened and 24 subjects completed the study. The FDA investigator performed a complete review of records for the 24 subjects who completed the study. The review included subject eligibility, source documents, case report forms, and data listings of

efficacy endpoints. An audit of all 26 informed consent forms was conducted.

b. Limitations of inspection: None.

c. General observations/commentary:

The data audit encompassed a review of original source documents and sponsor-provided electronic data listings. For four subjects (b) (6) the audit revealed instances of discrepancies between the primary efficacy variable data contained in the original subject diaries (original source documents) and the data provided by the sponsor in the electronic data listings. Specifically, where discrepancies were found, the subjects' "on" or "off" status (primary efficacy variable) recorded in the original subject diaries was not correctly represented in the sponsor-provided electronic data listings. All of the discrepancies involved subjects who received the test article. These discrepancies were not found to be site-specific deficiencies as no data entry was done at the study site. The original subject diaries were sent from Dr. Struck's site directly to the sponsor.

For Subject (b) (6) primary efficacy variable data discrepancies were noted between the sponsor's data listings and the following subject diary entries on 6/6/02: 6:00 AM, 3:00 PM, 3:30 PM, 4:00 PM, 6:00 PM, 6:30 PM, 12:00 AM, 12:30 AM, 1:00 AM, 1:30 AM, 2:00 AM, 2:30 AM, and 3:00 AM. On 6/20/02, discrepancies were noted at 12:00 PM, 12:30 PM, 1:00 PM, 1:30 PM, 2:00 PM, 2:30 PM, 3:00 PM, 3:30 PM, 4:00 PM, 4:30 PM, 5:00 PM, 5:30 PM, 11:00 PM, 11:30 PM, 2:30 AM, 3:00 AM, 3:30 AM, 4:00 AM, 4:30 AM, 5:00 AM, 5:30 AM, and 6:30 AM. Additionally, there were discrepancies between the sponsor's data listings and diary entries on 6/21/02 at 3:00 AM, and on 7/21/02 at 12:00 AM, 12:30 AM, 1:00 AM, 1:30 AM, 2:00 AM, 2:30 AM, 3:00 AM, 3:30 AM, 4:00 AM, 12:30 PM, 1:00 PM, 1:30 PM, 2:00 PM, and 2:30 PM.

For Subject (b) (6) primary efficacy variable data discrepancies were noted between the sponsor's data listings and the following 7/18/02 diary entries: 7:00 AM, 7:30 AM, 10:30 AM, 11:00 AM, 11:30 AM, 1:00 PM, 1:30 PM, 2:00 PM, 2:30 PM, 3:00 PM, 3:30 PM, 4:00 PM, 5:00 PM, 5:30 PM, 6:00 PM, 6:30 PM, 7:00 PM, 7:30 PM, 10:30 PM, 11:00 PM, 11:30 PM, 12:30 AM, 1:00 AM, 1:30 AM, 2:00 AM, 2:30 AM, 3:00 AM, 3:30 AM, 4:00 AM, 5:00 AM, 5:30 AM, and 6:00 AM. Discrepancies were also found between the sponsor's data listings and the subject diary entries on 7/19/02 at 1:30 AM, 2:00 AM, 2:30 AM, 3:00 AM, 3:30 AM, 5:00 AM, 5:30 AM, 6:00 AM, 6:30 AM, 7:00 AM, 1:00 PM, 1:30 PM, 2:00 PM, 2:30 PM, 3:00 PM, 3:30 PM, 5:00 PM, 5:30 PM, 6:00 PM, 6:30 PM, and 7:00 PM, on 8/1/02 at 1:00 AM, and on 8/2/02 at 10:30 AM. Additionally, discrepancies were noted between the sponsor's data listings and subject diary entries on 8/20/02 at 12:30 AM, 1:00 AM, 1:30 AM, 2:00 AM, 2:30 AM, 3:00 AM, 3:30 AM, 4:00 AM, 4:30 AM, 5:00 AM, 5:30 AM, 6:00 AM, 12:30 PM,

1:00 PM, 1:30 PM, 2:00 PM, 2:30 PM, 3:00 PM, 3:30 PM, 4:00 PM, 4:30 PM, 5:00 PM, 5:30 PM, and 6:00 PM, and on 9/29/02 at 5:30 PM.

For Subject (b) (6) a primary efficacy variable data discrepancy was noted between the sponsor's data listing and the diary entry at 6:00 PM on 9/9/02. Lastly, for Subject (b) (6) a discrepancy between the sponsor's data listing and the subject diary entry was found in the 4:30 AM entry on 8/5/02.

Recommendation: In general, the study appears to have been conducted adequately, and no site specific regulatory violations were noted. However, the Division of Neurology Products should evaluate the significance and impact, if any, of the discrepancies in primary efficacy data for Subjects (b) (6) on data acceptability. Other than the data discrepancies cited above, the data generated by this site appear acceptable in support of the respective indication.

(2) Dr. Dee Silver, Site #74
La Jolla, CA

a. What was inspected?

Forty-three (43) subjects were screened, 39 subjects were enrolled and randomized, and 35 subjects completed the study. A complete review of records was performed for 20 subjects. The review included source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor. Additionally, the inspection encompassed an audit of all 43 subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

In general, the study appears to have been conducted in compliance with protocol-specified requirements, with the exception of three subjects who did not meet protocol inclusion/exclusion criteria. Subjects (b) (6) had documented histories of carcinoma within five years of study enrollment, but were not excluded from study participation in violation of the protocol. Subject (b) (6) was not on a stable regimen of levodopa/carbidopa for at least four weeks prior to randomization, in violation of the protocol inclusion criteria. Overall, however, data in sponsor-provided data listings were supported by data in source documents and case report forms, and no deficiencies related to data validation were cited.

Recommendation: The Division of Neurology Products should evaluate the significance and impact, if any, of the above subjects' participation in the study given that they did not meet inclusion/exclusion criteria. Otherwise, data from this site appear acceptable for use in support of this NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, and received the assigned study medication. With regard to data acceptability, for Dr. Struck's site, the Division of Neurology Products should evaluate the significance and impact, if any, of the discrepancies in primary efficacy data for Subjects (b) (6) on data acceptability. At Dr. Silver's site, the review division should determine the significance and impact, if any, of three subjects' (Subject (b) (6)) participation in the study who did not meet inclusion/exclusion criteria. Other than the findings mentioned above, data generated from these sites reportedly capture primary efficacy endpoints as specified in the protocol, and appear acceptable for use in support of NDA 22-075.

{See appended electronic signature page}

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