CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209241Orig1s000

Trade Name:	INGREZZA capsules
Generic or Proper Name:	Valbenazine
Sponsor:	Neurocrine Biosciences, Inc.
Approval Date:	April 11, 2017
Indication:	A vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209241

NDA APPROVAL

Neurocrine Biosciences, Inc.
Attention: Kristine Kim, M.S.
Manager, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) dated August 11, 2016, received August 11, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ingrezza (valbenazine) 40mg Capsules.

This new drug application provides for the use of Ingrezza (valbenazine) 40mg Capsules for the treatment of tardive dyskinesia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We note that your April 10 and 11, 2017, submissions include final printed labeling (FPL) for your: package insert and patient package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your April 5, 2017, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Valbenazine was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable, because most of the products that cause tardive dyskinesia (older antipsychotic agents) are used less commonly in pediatric patients. Additionally, adolescent patients who might develop tardive dyskinesia generally remit after discontinuation of the antipsychotic.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the serious risk of toxicity due to altered metabolism of the major circulating moieties (NBI-136110) as a result of CYP2B6 enzyme induction.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3177-1 Conduct an in vitro study to assess the induction potential of NBI-136110 on CYP2B6 enzyme.

The timetable you submitted on April 5, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2017
Study Completion:	07/2018
Final Report Submission:	12/2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of toxicity due to the increased metabolite (NBI-98782) in CYP2D6 poor metabolizers and patients with severe renal and hepatic impairment. Additionally, only a clinical trial will be sufficient to identify an unexpected serious risk of short-term withdrawal symptoms following valbenazine discontinuation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3177-2 Conduct a pharmacokinetic trial to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites, either in the presence of a strong CYP2D6 inhibitor or in subjects who are CYP2D6 poor metabolizers (PMs).

The timetable you submitted on April 5, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2017
Trial Completion:	12/2018
Final Report Submission:	08/2019

3177-3 Conduct a pharmacokinetic trial to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.

The timetable you submitted on April 5, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2017
Trial Completion:	12/2018
Final Report Submission:	08/2019

3177-4

Evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine. Implement the following assessments in a current or future study in which subjects will receive valbenazine treatment (40 and 80 mg/day) for at least four consecutive weeks: Administer withdrawal scales, assess for withdrawal-related AEs, and monitor vital signs on the last day of treatment,

day 1 off-treatment, every other day thereafter for the first week, and then 2-3 times weekly for two additional weeks.

The timetable you submitted on April 5, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2018
Trial Completion:	01/2019
Final Report Submission:	01/2020

For PMRs 3177-1, 3177-2, and 3177-3 submit clinical protocols to your IND 111591 with a cross-reference letter to this NDA. For PMR 3177-4, submit your clinical protocol to IND (b) (4). Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii) . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3177-5 Perform a randomized controlled trial to assess whether a higher dose would confer additional therapeutic benefit. You may consider a design in which subjects with an inadequate response to valbenazine 80 mg are randomized to continue the 80 mg dose or receive a higher dose. Depending on findings from the clinical pharmacology study evaluating the effect of CYP2D6 inhibition on plasma concentrations, CYP2D6 poor metabolizers may be excluded from this

trial to reduce the risk for exposure-related adverse events such as QT prolongation.

The timetable you submitted on April 5, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	03/2019
Trial Completion:	03/2023
Final Report Submission:	03/2024

3177-6 To better assess the persistence of valbenazine treatment for TD, perform a trial in which subjects who have demonstrated an adequate response to valbenazine are randomized to receive placebo or continue their current dose. Subjects should be stratified based on whether they are continuing to take an antipsychotic. A significant proportion of subjects should no longer be taking antipsychotics in order to assess the potential for differential persistency.

The timetable you submitted on April 5, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2018
Trial Completion:	01/2021
Final Report Submission:	01/2022

3177-7 To provide evidence as to whether improvement on the AIMS total dyskinesia scale translates into long-term functional improvements, perform a trial to address this question. Given the functional heterogeneity of patients with TD, it will be important to select an appropriate patient population and outcome measures. As discussed at the late-cycle meeting, one potential measure could assess social isolation.

The timetable you submitted on April 5, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2018
Trial Completion:	04/2020
Final Report Submission:	04/2021

Submit clinical protocols to your IND 111591 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol,"**

"Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

OTHER

1. We remind you of your December 23, 2016, and February 8, 2017, commitments to add bulk density, tapped density and optical rotation tests and acceptance criteria to the drug substance specification. We request that you submit these changes in a prior approval supplement within six months of when data is available on (b) (4) drug substance batches.

2. We determined that your stability data support an 18-month drug product expiry period.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
04/11/2017