CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Recommend Approval

NDA 209241
Review #1

Drug Name/Dosage Form	Ingrezza (valbenazine) Capsules
Strength	40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neurocrine Biosciences, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
N-002	11 AUG 2016	All
N-005	1 SEP 2016	Drug product.
N-011	26 OCT 2016	Drug substance
N-018	23 DEC 2016	All
N-031	8 FEB 2017	Drug substance.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	OPQ/ONDP/DNDAPI/NDBI
Drug Product	Rao Kambhampati	OPQ/ONDP/DNDPI/NDPBI
Process	Chunsheng Cai	OPQ/OPF/DPAI/PABI
Microbiology	N/A	
Facility	Steven Hertz	OPQ/OPF/DIA/IABI
Biopharmaceutics	Ta-Chen Wu	OPQ/ONDP/DB/BBI
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMBI
Environmental Analysis	Jim Laurenson	OPQ/ONDP
Application Technical Lead	David Claffey	OPQ/ONDP/DNDPI/NDPBI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: LoAs provided for various packaging components (DMFs (b) (4) . Data in application adequate to support their use.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	111591	Original IND

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective.

Recommend that the following be added to the action letter:

1. We remind you of your 23 DEC 2016 and 8 FEB 2017 commitments to add bulk density, tapped density and optical rotation tests and acceptance criteria to the drug substance specification.
2. We determined that your stability data support a (b)(4)-month drug product expiry period.

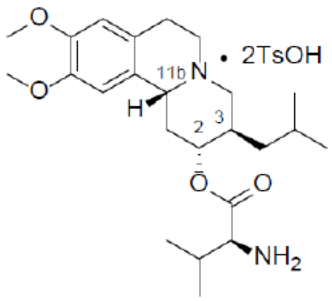
II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Treatment of Tardive Dyskinesia***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***80 mg***
Alternative Methods of Administration	***None***

Quality Assessment Overview

Drug substance basics: The drug substance, valbenazine tosylate is an NME. Note that, despite its USAN adopted name, valbenzine tosylate is chemically a ditosylate. Chemically, it is essentially a valine ester of a reduced form of tetrabenazine. It has four chiral centers.



Several polymorphic forms exist, but [redacted] was chosen for development. Impurity [redacted] a known human metabolite, was identified as [redacted] were found acceptable.
The drug substance has good water solubility across a range of pHs [redacted] and was found to be slightly [redacted] hygroscopic.
The drug substance multistep manufacturing process was found to be acceptable. [redacted] Drug substance quality, including isomeric purity, is assured via process understanding, IPCs, starting material and intermediate controls and the drug substance specification. The drug substance specification is typical for a small molecule. Additional controls are in place for drug substance isomers by [redacted]. Additional assurance of isomeric purity will be provided by [redacted] after data on [redacted] drug substance batches are collected. Given the drug product manufacturing issues, a commitment to add a bulk/tapped density specification was similarly provided. A process-specific justification was provided to support the absence of a quantitative specification for the tosylate counterion.
The commercial manufacturer will be, [redacted] This site was found to be acceptable by the OPQ facilities team. It is noted that [redacted] of the registration drug product batches used drug substance from another manufacturer [redacted] The applicant intended [redacted] however this proposal was not part of the final application. [redacted]

Drug product basics: The drug product is a single strength, 40 mg, immediate-release purple/white Size 1 capsules. Each capsule contains 73.0 mg of valbenazine tosylate. The labeled strength is based on the equivalent amount of valbenazine base. The drug product capsule contains a powder consisting of [redacted]% w/w drug substance, [redacted]% mannitol [redacted]% starch ([redacted] and [redacted]% w/w of both silica ([redacted] and magnesium stearate ([redacted] Two drug product packaging configurations were proposed: HDPE bottles (30-count in 60 ml and 90-count in 120 ml) and physician sample [redacted] blisters.
The drug product manufacturing process steps include [redacted] The process was transferred to a commercial manufacturing site and [redacted] batches were manufactured at [redacted] sites. Commercial manufacturing will take place at [redacted] The data support a [redacted] month expiry period rather than the proposed [redacted] month expiry period.

Other critical OPQ review team findings:

- The OPF facilities review team found each of manufacturing and testing sites acceptable for the functions listed in the application.
- The environmental assessment (EA) team found the categorical exclusion claim from an EA accordance with 21 CFR Part 25.31(b) to be acceptable.

- The Biopharmaceutics review team found the proposed dissolution method acceptable for release and stability testing. Although a BCS designation was not requested the biopharmaceutics team considered the drug product more a Class I, although the applicant more conservatively considered it a Class III due to lack of data on bioavailability.
- The drug substance, drug product and manufacturing process review teams recommended approval.

Main Quality Review Issues –

Differences between the clinical and commercial drug product: There are significant differences between the (b) (4) drug product used in Phase 3 studies and the proposed commercial product – (b) (4) . A bioequivalence study successfully bridged these formulations. In vitro performance results, including dissolution data, supported this bridge.

(b) (4)

Drug product degradation and expiry period: Very limited drug product stability data was available from batches from the proposed ((b) (4) commercial site - just six months long-term and accelerated conditions for the three commercial-scale batches in bottles (and three months in blisters). Supportive data, through 12 months long-term storage were provided for three commercial-scale batches at a previous manufacturing site, (b) (4) As the (b) (4) batches were (b) (4) identical to the commercial product, their stability data were used to support the expiry period. Significant decreases in drug product assay were observed in all long-term storage studies, however all results remained within specified limits. Statistical analysis of the data from the (b) (4) site supported a (b) (4) month expiry period. Although the process review team found the product/process in both sites to be comparable, the drug product reviewer determined that the 6-month data from the (b) (4) commercial site and the 12 months data from the former site ((b) (4) support a (b) (4)-month, rather than the requested (b) (4)-month, expiry period.

The following was added to the Late Cycle Meeting minutes:

We determined that your stability data support a (b) (4)-month drug product expiry period. This is due to the limited stability data from the commercial drug product drug product site (six months in bottles and three months in blisters). Further, only one of the three primary drug product batches manufactured at the (b) (4) site used drug substance from the proposed commercial drug substance manufacturing site. We acknowledge that some of your statistical models used the 12-month (b) (4) supportive data to demonstrate that the assay would not go below the acceptance criterion until (b) (4) months. However these batches were not manufactured at the proposed (b) (4) commercial site and some models found batches failing near the (b) (4) month time point. It was in the context of the totality of this information that the (b) (4)-month expiry period was found acceptable; however the expiry may be extended based on real-time data from the primary (b) (4) stability batches.

B. Special Product Quality Labeling Recommendations (NDA only)

None.

C. Final Risk Assessment (see Attachment)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Drug substance appears relatively stable. The relatively high acceptance criterion for individual impurities will require evaluation by pharm/tox and the need for the higher limits by OPQ	L	(b) (4)	Acceptable	
Physical stability	(b) (4) form	M		Acceptabl	Look out for

(Solid State)	needs control Bulk density critical for manufacturabilit y		(b) (4)	e	additional bulk density and optical rotation tests that will be added to the drug substance spec (see executive summary above)
Microbial Limits	Monitoring at release and stability	L	Found to be acceptable.	Acceptabl e	
(b) (4)		H	See above.	Acceptabl e	This is a critical issue with potential impact on patients. (b) (4) issues were found during development.
Dissolut ion	Impact of formulation change from clinical to Phase III needs evaluation. (b) (4)	M	BE bridging studies found acceptable. In vitro data including dissolution data found supportive of the change.	Acceptabl e	

ENVIRONMENTAL ANALYSIS

Summary: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The cited categorical exclusion is appropriate for the estimated amount of drug to be produced for direct use, and the required statement of no extraordinary circumstances was included. During the investigational new drug (IND) phase, the applicant provided FDA requested additional information due to the status of the active ingredient as a new molecular entity (NME) and the potential for hormonal activity, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.

R Regional Information

Environmental Analysis

Valbenazine tosylate (valbenazine) is a novel, orally active inhibitor of vesicular monoamine transporter 2 (VMAT2) for the treatment of tardive dyskinesia (b) (4) VMAT2 plays a role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

During the IND phase, for IND 111591, the applicant noted in a written submission for a February 6, 2016 Type B meeting that, based on current market projections, the maximum annual production of valbenazine for all dosage forms in the next 5 years will be approximately (b) (4) kg, which converts to an expected introduction concentration (EIC) of approximately (b) (4) ppb. The applicant asked whether FDA agreed that this concentration would qualify the NDA for a categorical exclusion from an EA. FDA responded that while the NDA would appear to qualify for the exclusion based on 21 CFR 25.31(b) (for drugs that increase in use but have an EIC less than 1 ppb), the lowest-no-observed-adverse-effect level (NOAEL) in the applicant's Toxicology Written Summary, (b) (4) mg/kg/day (Section 2.6.6.4.1), results from a reproductive/fertility and early embryonic development study in rats and needs to be considered within the context of the EIC and FDA's recently (at the time) published draft environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid (E, A, or T) activity (now final at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf).

The applicant responded by noting that their EIC was very conservative, with no correction for the salt form of the drug, actual market penetration data, and reduction in the environment such as from metabolism prior to excretion and dilution and degradation in the environment. In addition, reproductive/developmental toxicity in the rat was noted as being associated with a

blood AUC (area under the plasma concentration time curve) with a several orders of magnitude margin to aquatic organism AUC at the EIC. The sponsor asked whether providing such data would be sufficient for supporting the claim for the categorical exclusion. FDA agreed that any such fate and extrapolation or "read-across" toxicity data would be useful for providing the additional support needed for the categorical exclusion, and that such data are in line with the draft guidance at the time.

For the NDA, the applicant requested a claim for a categorical exclusion from an EA, per 21 CFR 25.31(b). The applicant provided an updated calculation for EICs of two substances to support this claim in section 3 of Appendix A of the categorical exclusion submission, CTD section 1.12.14. The EICs are (b) (4) and (b) (4) parts per trillion (ppt) for valbenazine and its active metabolite, NBI-98782, respectively. The applicant noted that these concentrations are well below the 1 ppb cutoff established by 21 CFR 25.31(b). The concentrations were calculated using fraction biodegraded during wastewater treatment, fractions of drug or metabolite excreted unchanged in urine and feces, and fraction of the active moiety in the drug compound salt. The applicant noted that these calculations do not account for additional removal of the compounds of interest through sorption to biosolids during wastewater treatment.

Expected environmental concentrations (EECs) also were calculated based on the mixing of treated effluent with receiving waters. A dilution factor of 10 was applied to the EIC to estimate EECs of (b) (4) ppt for valbenazine and (b) (4) ppt for NBI-98782. The applicant noted that these two substances would have to be equivalent in toxicity to the synthetic estrogen, 17α-ethinylestradiol, to approach an adverse effect threshold for aquatic organisms, which the applicant considered very unlikely considering the lack of evidence of estrogenic, androgenic, or thyroid activity. This evidence is addressed in section 2 of Appendix A of the categorical exclusion submission. Briefly, the reproductive/developmental toxicity study referred to by FDA results in a NOAEL that is associated with ptosis (i.e., squinted eyes) and/or decreased activity in the rat, which is an expected pharmacological effect of monoamine depletors such as valbenazine and the structurally related tetrabenazine. Such lethargy and decreased activity, it is argued, could readily explain the slight reduction in fertility seen at the highest dose. In addition, no histopathological changes in E, A, or T-sensitive tissues that might indicate E, A, or T activity has been seen in any of the entire battery of preclinical studies in mice, rats, or dogs.

The applicant makes several other arguments regarding the observed pharmacological effects, such as by noting that the effect on prolactin levels is responsible for the effect of valbenazine on mammary gland hyperplasia in mice and rats, while effects typical of estrogenic stimuli, such as uterine fluid retention, estrus conversion, increased uterine weight, uterine stromal cell proliferation, or uterine epithelial cell height were not seen with valbenazine.

As a supplemental line of evidence, the aquatic EECs were compared in section 3 of Appendix A of the categorical exclusion submission to concentrations associated with a lack of adverse effects in mammalian toxicity studies. Using a bioconcentration model and assumptions, concentrations of valbenazine and NBI-98782 in fish tissue were estimated as (b) (4) and (b) (4) µg/kg, respectiverly. In comparison, the applicant calculated AUC NOAELs as low as (b) (4) µg/kg for valbenazine and (b) (4) µg/kg for NBI-98782, which resulted in margins of safety (MoS) of (b) (4) and (b) (4) respectively.

The applicant concluded that based on this information, valbenazine shows no E, A, or T activity, and that concentrations of valbenazine and its active metabolite estimated in fish tissue (based on highly conservative assumptions) are 2 to 3 orders of magnitude lower than a comparable mammalian NOAEL. A categorical exemption from the requirement for an environmental assessment is warranted, the applicant states, and no extraordinary circumstances exist.

Reviewer's Assessment

The categorical exclusion claim is appropriate for the anticipated amount of drug to be used, the calculations appear accurate, and an adequate statement of no extraordinary circumstances is present. The data provided by the applicant support the claim for the categorical exclusion from an EA, with the possible exception of the 10-fold dilution factor used to develop a EECs. This dilution factor is not relevant in the increasing number of municipalities for which most or all of the effluent from a sewage treatment plant form the primary flow of the receiving stream or river. Nevertheless, using EECs without this dilution factor still result in MoS of 24 and 190 for valbenazine and NBI-98782 in fish tissue, respectively, which are acceptable given the lack of E, A, or T signals and the several conservative assumptions contained in the analysis (e.g., sorption to biosolids during wastewater treatment, degradation in the environment).

The claim for a categorical exclusion from an EA is acceptable.

Primary EA Reviewer Name and Date: Jim Laurenson, 2/2/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 2/2/2017

Michael Furness

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James Laurenson

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LABELING

R Regional Information

1.14 Labeling

Immediate Container Labels

1) 30-Count bottle label:

2) 90-Count bottle label:

3) 5-Count unit dose blister pack label:

(b) (4)

Reviewer's Assessment: Acceptable from the CMC perspective. The above two bottle labels contain all the required information. Strength is based on the amount of free base present in the capsule. The API is a tosylate salt and the labels contain a statement for the equivalent amount of the free base present in each capsule. The unit dose blister pack of 5 count is used as physician sample only and it is secondary packaged in a carton (see below), which contains all the required information.

Carton Labeling

5-Count unit dose blister pack carton label:

(b) (4)

[redacted]

Reviewer's Assessment: Acceptable from the CMC perspective. Carton is used for packaging physician sample blister packs only. Bottles are not packaged in cartons.

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D., 2/8/17

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D., 2/8/17

David Claffey

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Rao Kambhampati

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BIOPHARMACEUTICS

Product Background:

NDA: 209241-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: INGREZZA™ (valbenazine, NBI-98854) Capsules/ 40 mg

Route of Administration: Oral

Applicant Name: Neurocrine Biosciences

Review Summary:

The Biopharmaceutics review for this submission is focused on the evaluation and acceptability of the proposed dissolution methodology, validation and discriminating ability of the dissolution method, and acceptance criteria for INGREZZA™ (Valbenazine, NBI-98854) Capsules (immediate-release).

The proposed QC dissolution method [USP Apparatus 2 (paddle) with stainless steel wire helix sinkers at 50 rpm, 900mL of 0.1M HCl pH 1.2] and acceptance criteria [Q = (b)(4)% at 20 min for Valbenazine] for the routine QC testing of Valbenazine oral capsules during batch release and stability testing are both ACCEPTABLE.

Drug release from the proposed commercial (b)(4) gelatin capsules and the clinical (b)(4) capsules was rapid (i.e., > (b)(4)% in (b)(4) min, but essentially nearly complete at (b)(4) min for the proposed gelatin capsules and at (b)(4) min for the clinical (b)(4) capsules) and complete in the proposed QC dissolution medium. The proposed dissolution method was shown to have potential discriminating power for batches with potentially (b)(4) formulations with respect to disintegrant level, as well as for the gelatin (b)(4)

The Applicant did not submit a formal request for BCS designation for the drug substance or drug product. However, Valbenazine behaves like a BCS Class-1 drug based on its characteristics of high-solubility across the physiologic pH range, high permeability, relatively high lipophilicity, and having an absolute bioavailability of approximately 49% with extensive metabolism. Since oral absorption of ≥85% was not unequivocally demonstrated, the Applicant concluded that Valbenazine may be considered a BCS Class 3 drug to be more conservative.

Relative bioavailability of the to-be marketed and clinical trial formulations were compared and shown to be bioequivalent (refer to OCP review). The formulations used in pivotal clinical studies (b)(4)) and the proposed commercial drug products (with (b)(4) gelatin capsules) are (b)(4) Given that, comparative dissolution testing is not considered to be critical at this point in view of the in vivo bridging results and the

rapid in vitro drug release. Similar dissolution profiles of (b) (4) lots and (b) (4) registration lots were also observed.

From the Biopharmaceutics perspective, NDA 209241 for Valbenazine Capsules, 40 mg, is recommended for APPROVAL.

The approved dissolution method and acceptance criterion are summarized as follows:

Parameters	Value
Apparatus	USP Apparatus II (paddles) with stainless steel wire helix sinkers
Dissolution Media (Tier 1)	0.1M HCl pH 1.2
Dissolution Media (Tier 2)	0.1M HCl pH 1.2 (b) (4)
Dissolution Volume	900 mL
Rotation Speed	50 rpm
Temperature	37°C ± 0.5 °C
Sample Analysis	HPLC/UV ((b) (4) nm)
Acceptance Criterion	Q = (b) (4)% in 20 minutes

List Submissions being reviewed (table):

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Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment:

The Applicant did not submit a formal request for BCS Class 1 or Class 3 designation for the drug substance or drug product. Valbenazine exhibits characteristics of high-solubility across the physiologic pH range, high permeability, relatively high lipophilicity, and having an absolute bioavailability of approximately 49% (oral absorption of ≥85% was not unequivocally demonstrated), the Applicant concluded that Valbenazine may be considered a BCS Class 3 drug to be more appropriate, as the existing data do not support an unambiguous BCS Class 1 classification. The rationale is summarized in the sections below.

Solubility:

Valbenazine is considered 'highly soluble' (40 mg free base is soluble in 250 mL of aqueous media over the pH range of (b) (4); drug substance (ditosylate salt) solubility >10 mg/mL for

the highest 80mg dose across the physiologic pH range; rapid and complete dissolution in biorelevant media; see Table 1). Changes in [redacted] (b) (4) formulations did not appear to impact the relative oral bioavailability of Valbenazine, as supported by in vivo parent drug and metabolite data (refer to OCP review).

Table 1: Equilibrium solubility of Valbenazine tosylate in bio-relevant media

Media and Initial pH	Final pH	Solubility (mg/mL)	USP Descriptive Solubility	BCS (40 mg Dosage Units/250 mL)
pH 1.2, 0.1 M HCl	1.2	12	Sparingly Soluble	75
pH 1.6, FaSSGF	1.7	12	Sparingly Soluble	75
pH 2.0, 0.01 N HCl	2.1	11	Sparingly Soluble	69
pH 4.5, Acetate Buffer	4.5	11	Sparingly Soluble	69
pH 5.0, FeSSIF	5.0	20	Sparingly Soluble	125
pH 5.8, FaSSIF	5.8	18	Sparingly Soluble	112
pH 6.8, Phosphate Buffer	6.1	13	Sparingly Soluble	81

Permeability:

Valbenazine may be considered highly permeable and is not a substrate of P-gp or BCRP efflux transporters in Caco-2 cells (see Table 2). Valbenazine is characterized by relatively rapid absorption (with possible involvement of active uptake), with short median Tmax of approximately 0.75 hour for peak drug concentration after oral administration, which reflects the in vitro finding as well.

Table 2: In vitro permeability of NBI-98854 (Valbenazine)

Test Article	Test System	P_{app} (10^{-6} cm/sec)[a]		Ratio P_{app} (b>a)/(a>b)
		apical>basolateral (a>b)	basolateral >apical (b>a)	
NBI-98854	Caco-2	30.4	11.9	0.4
	MDCK-MDR1	47.9	26.5	0.6

Results of human a mass-balance study, however, showed an absolute bioavailability of approximately 49%; extensive metabolism, 60% of drug-related material being excreted in urine (1.8% excreted unchanged in urine), and 1.8% being excreted unchanged in feces. Oral absorption of ≥85% was not unequivocally demonstrated, thus the Applicant considered the drug as a BCS Class-3 drug to be conservative, although Valbenazine showed most characteristics of BCS Class-1 drug.

Dissolution:

Formulations used in clinical trials and for commercialization, as well as salt forms of the API, were shown to have no significant impact on the dissolution. Drug release demonstrated in in-vitro dissolution testing of the proposed commercial gelatin capsule (i.e., > (b) (4) % in (b) (4) min or

nearly complete in (b) (4) min) and the clinical (b) (4) capsule was rapid (i.e., > (b) (4)% in (b) (4) min) and complete. The characteristics of rapid dissolution appear to correspond with relatively rapid oral absorption of Valbenazine in humans, likely to occur in the upper gastrointestinal tract, in view of the very short Tmax (0.75 hour) after oral administration.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

The Applicant developed a dissolution method in accordance with USP<1092>, FDA "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms", and ICH Q6A, for Valbenazine immediate-release capsules. The proposed method employed USP Apparatus 2 (paddles) with stainless steel wire helix sinkers at 50 rpm rotation speed, with 900 mL of 0.1 M HCl pH 1.2 at 37 ± 0.5°C, and the HPLC/UV detection for sample analysis.

Dissolution Method Development:

(b) (4)

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Steven Hertz

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