CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215211Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **May 4, 2023**

From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: **To the IQA for NDA 215211 Prior to Final Action**

Subject: **Review of the CMC Amendment Submitted to the Application Prior to the final Action on NDA 215211: This application is still recommended for approval after the review of the CMC amendment Dated December 12, 2022**

In the Integrated Quality Assessment #1 (IQA #1) for NDA 215211 dated May 18, 2022, this application was recommended for approval from the OPQ perspective. Since the drug product in this application is to be co-administered with a drug product, cipaglucosidase being reviewed under BLA 761204 for which the review has not been completed due to delays associated with inspection of the manufacturing site, the final approval action on NDA 215211 has not been taken. Meanwhile the applicant of this NDA submitted a CMC amendment on December 12, 2022. This amendment included updates to the manufacturing, drug substance, and drug product (dissolution method). The drug substance update was provided in DMF (b) (4) The drug substance update has been captured separately as the DMF review and the DMF has been found to be still adequate to support the approval of this application from the drug substance perspective. The DMF review will not be attached to this memorandum. The reviews of this CMC amendment for manufacturing and drug product updates are attached below.

Therefore, from the OPQ perspective this application is still recommended for **approval.**

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Memorandum

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

Date: **Jan 6, 2023**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Hamid Shafiei, Ph.D.**
SPQA, ONDP/Division II/Branch IV

To: **Review #1 of NDA 215211**

Subject: **Review of Amendment 0025**

The applicant provided a revised dissolution method in this amendment. The revision changed the dissolution sampling time from three time points 10 min. 15 min. and 30 min. to 15 min. The sampling time at 15-min. time point is specified in the acceptance criterion in the proposed drug product specification. The method procedure and method validation for the dissolution are adequately updated.

Recommendation:

This NDA is recommended for approval from the drug product perspective.

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 1/06/2023 01:17:25PM
GUID: 508da7210002a030e76df4f60ccd142a

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 1/06/2023 01:40:22PM
GUID: 507d824300005f344cf8b5e5989f0057

26 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
05/04/2023 08:02:25 AM

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215211
Assessment 1

Drug Product Name	Opfolda (miglustat)
Dosage Form	Capsules
Strength	65 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Amicus Therapeutics USA, LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	07/29/2021	All
Proprietary Name Request	08/03/2021	All
Quality Information	08/27/2021	ONDP
Quality Information	08/30/2021	ONDP
Proprietary Name Request	09/22/2021	All
Response to Quality Information Request	10/28/2021	OPMA
Response to Quality Information Request	11/05/2021	ONDP
Response to Quality Information Request	11/19/2021	ONDP
Clinical Safety Update and Draft Labeling	11/23/2021	All
Response to Information Request – Multiple Category	12/03/2021	OPMA and Nonclinical
Response to Quality Information Request	12/13/2021	OPMA
Nonclinical Information Amendment	01/21/2022	Nonclinical
Draft Labels and labeling	02/24/2022	All
Response to Clinical Information Request	03/15/2022	Clinical

Container and Carton Labels	03/17/2022	All
Draft Labeling	04/19/2022	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
Drug Product	Zhengfang Ge, Ph.D.	Hong Cai, Ph.D.
Manufacturing	Mesfin Abdi, Ph.D.	Vaikunth Prabhu, Ph.D.
Microbiology	Mesfin Abdi, Ph.D.	Vaikunth Prabhu, Ph.D.
Biopharmaceutics	Kamrun Nahar, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Zhengfang Ge, Ph.D.	Hong Cai, Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, miglustat and the drug product, OPFOLDA® (miglustat) Capsules, 65mg.
- The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved.
- The applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **approval** with the expiration dating period of **24 months** for 4-count and 100-count capsules packaging configurations and **36 months** for 24-count capsules packaging configuration.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Amicus Therapeutics US, LLC has submitted the 505(b)(2) new drug application for OPFOLDA® (miglustat) Capsules, 65mg. OPFOLDA capsules are intended as an enzyme stabilizer that in conjunction with POMBILITI™, a hydrolytic lysosomal glycogen-specific enzyme, is indicated for (b) (4) (b) (4) The recommended dosage for patients weighing greater than 50kg is 4 capsules (260mg of miglustat) and for patients weighing between 40kk to 50kg is 3 capsules (195mg of miglustat). OPFOLDA capsules should be taken on an empty stomach and patients should eat 2 hours before and 2 hours after taking the capsules. OPFOLDA capsules should be taken 1 hour (b) (4) (b) (4) before the start of the cipaglucosidase alfa–atga infusion.

Pompe disease is a rare autosomal recessive genetic disorder caused by mutations in the gene that encodes human acid α-glucosidase (GAA), an enzyme responsible for the breakdown of lysosomal glycogen.

Compromised or reduced function of this enzyme results in lysosomal glycogen accumulation and progressive disruption of cellular function.

Miglustat is an N-alkylated iminosugar, a synthetic analog of D-glucose. It is a glucosylceramide synthase inhibitor which was first approved on July 31, 2003 (NDA 021348) as the active ingredient of ZAVESCA indicated as monotherapy for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access). However, miglustat in this application has been pharmacologically classified as enzyme stabilizer.

To be marketed OPFOLDA® (miglustat) Capsules, 65mg will be packaged as 4-count and as 24-count capsules in 40cc as well as 100-count capsules in 120cc HDPE bottles with induction sealed child-resistant cap.

Capsules should be stored at 20°C to 25°C (68°F to 77°F) with excursion permitted from 15°C to 30°C (59°F to 86°F). Based on the stability data provided in the application expiration dating period of 24 months for 4-count and 100-count capsules packaging configurations and expiration dating period of 36 months for 24-count capsules packaging configuration have been granted.

Proposed Indication(s) including Intended Patient Population	Treatment of Pompe disease in patient 18 years of age and older
Duration of Treatment	As prescribed by a physician
Maximum Daily Dose	260mg for patients weighing greater than 50kg and 195mg for patients weighing between 40kg to 50kg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

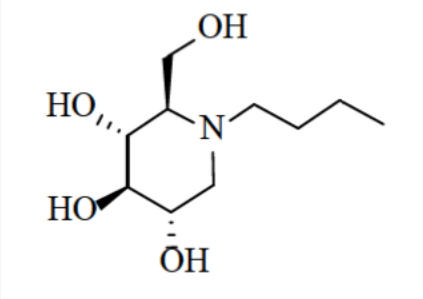
Drug Substance: Adequate

The drug substance, miglustat is an N-alkylated iminosugar and a synthetic analog of D-glucose. It is a glucosylceramide synthase inhibitor which aws first approved on July 31,2003 as the active ingredient of ZAVESCA (NDA 021348).

Miglustat is a white to off-white solid which is readily soluble in water, soluble in methanol but insoluble in n-heptane, dichloromethane, and ethyl acetate. A 1% solution of miglustat exhibits a pH of 8.7. The

calculated pKa values for the drug substance are 8.49 and 12.9. Miglustat has 4 chiral centers, and its chirality is well-controlled (b) (4) (b) (4) (b) (4)

Miglustat has the chemical name of (2R,3R,4R,5S)-1-butyl-2-hydroxymethyl)piperidine-3,4,5-triol, a molecular formula of C10H21NO4, a molecular weight of 219.28 and the chemical structure below:



Miglustat for this application is manufactured in accordance with current Good Manufacturing Process (cGMP) requirements (b) (4) (b) (4) The description of the manufacturing process for the miglustat manufactured (b) (4) (b) (4) is provided in DMF (b) (4) This DMF was recently reviewed by Dr. Rodger Farr on November 10, 2021 and found to be adequate. The description of the manufacturing process for the miglustat manufactured (b) (4) is provided in DMF (b) (4) This DMF was recently reviewed by the Drug Substance Reviewer, Dr. Jeffrey Medwid on January 3, 2022 and found to be adequate. Miglustat drug substance manufactured by both manufacturers is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest period of (b) (4) months for miglustat manufactured (b) (4) and (b) (4) months for miglustat manufactured (b) (4)

Relying on the Dr. Farr's review of DMF (b) (4) the review of DMF (b) (4) and the review of the information provided in the drug substance module of this application, the Drug Substance Reviewer, Dr. Jeffrey Medwid has found the drug substance information adequate to support the approval of this application from the drug substance perspective. Dr. Medwid's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

The drug product, OPFOLDA® (miglustat) Capsules, 65mg in conjunction with POMBILITI™, a hydrolytic lysosomal glycogen-specific enzyme, is

indicated (b) (4) (b) (4) (b) (4). Miglustat in this application has been pharmacologically classified as an enzyme stabilizer.

Each OPFOLDA® is a size 2 hard gelatin capsule that contains 65mg of miglustat as the active ingredient and microcrystalline cellulose, starch (pregelatinized maize), sucralose, magnesium stearate, and colloidal silicone dioxide as inactive ingredients. The inactive ingredients including components of the hard gelatin capsule shells are all compendial materials. Iron oxide is used (b) (4) The total iron content of each capsule is below the 5mg daily consumption by the patients per 21 CFR 73.1200 (c). The amounts of excipients used as the components of the drug product are below the currently approved limits listed in IID. Therefore, the proposed quantitative composition of the drug product is deemed acceptable.

OPFOLDA® capsules are manufactured (b) (4) in accordance with cGMP requirements, packaged in HDPE bottles with child-resistant caps, and tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its expiration period of 24 months for 4-count and 100-count capsules packaging configuration and 36 months for 24-count capsules packaging configuration. Adequate stability data that supports the proposed expiration dating periods have been submitted to the application.

The drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has found the information provided adequate to support the approval of this application from the drug product perspective. Dr. Ge's review is provided in the Drug Product Chapter of the IQA.

The applicant's request for the categorical exclusion from preparation of environmental assessment has also been reviewed by Dr. Ge. Dr. Ge has found the application for the categorical exclusion appropriate and has recommended granting the categorical exclusion to this application. Dr. Ge's review of the categorical exclusion is also provided in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC section of the PI labeling as well as immediate container labels have been reviewed by the Drug Product Reviewer, Dr, Zhengfang Ge. In her original review of the labeling/label dated January 5, 2022, Dr. Ge had identified CMC labeling/label deficiencies that needed to be addressed before this application could be recommended for approval from the

labeling/label perspective. The applicant submitted an amendment dated March 17, 2022, that has adequately addressed the deficiencies noted in Dr. Ge's original review. Therefore, based on the totality of the information submitted in the application and the amendment dated March 17, 2022, Dr. Ge has recommended the approval of this application from the labeling/label perspective. Dr. Ge's review of the labeling/label as well as her labeling/label review addendum dated April 18, 2022, is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

The manufacturing process for OPFOLDA® (miglustat) Capsules, 65mg includes (b) (4)

(b) (4)

The proposed facilities involved in the manufacture of the drug substance and drug product have been evaluated and accepted based on the facilities' profiles, history of compliance, and previous experience in the manufacture of similar products.

The manufacturing process as well as the manufacturing facilities involved in this application have been reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) Reviewer, Dr. Mesfin Abdi. Dr. Abdi has found the manufacturing process and the manufacturing facilities involved in this application adequate and has recommended the approval of this application from the manufacturing process and facilities perspective. Dr. Abdi's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The biopharmaceutics review for this application was mainly focused on dissolution method and bridging studies conducted to bridge early formulations such as powder in capsule to the formulation used in Phase 3 clinical trials and the formulation intended for commercial use.

The applicant has developed an in-house dissolution method using USP apparatus II (paddles) at 75rpm in 500mL of 0.1N HCl with proposed acceptance criteria of Q = (b) (4)% in 15 minutes. This dissolution method has been used as a means for the quality control test for the drug product release and stability. Although this method has not been shown to exhibit discriminating ability, due to high solubility of miglustat, the method is considered acceptable.

The applicant conducted comparative dissolution studies to bridge formulations used the early clinical trials, Phase 3 clinical trials, and the formulation intended for commercial use. The data from the comparative dissolution studies showed similar drug release for all formulations miglustat.

The biopharmaceutics section of this application has been reviewed by the Biopharmaceutics Reviewer, Dr. Kamrun Nahar. Dr. Nahar has concluded that the information provided in the biopharmaceutics section this application adequate to support the approval of this application from the biopharmaceutics perspective. Dr. Nahar's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

The drug product, OPFOLDA® (miglustat) Capsules, 65mg is a non-sterile solid dosage form product. Therefore, the review and evaluation of bioburden have been performed by the OPMA Reviewer, Dr. Mesfin Abdi. Dr. Abdi has found the bioburden information provided in this application adequate and recommended the approval of this application from the microbiology perspective. Dr. Abdi's review is captured in the Manufacturing Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
No high-risk attributes have been identified	No high-risk manufacturing processes have been identified	L	(b) (4)	Acceptable	None

D. List of Deficiencies for Complete Response

None

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 5/18/2022 11:09:30AM
GUID: 507d824300005f344cf8b5e5989f0057

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	November 10, 2021	Latest Review by Rodger Farr, Ph.D.
	II			Adequate	January 3, 2022	Latest Review by Jeffrey Medwid, Ph.D.
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information

(b) (4)		(b) (4)			Provided in the NDA
	III		_____	_____	Adequate Information Provided in the NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	021348	Cross-referenced application

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

68 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	OPFOLDA	**Adequate**
Established name(s)	**(miglustat), capsules**	**Not Adequate** remove comma between establish name and dosage form
Route(s) of administration	oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 65 mg	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2.1 Instructions for Administration

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)	**Adequate**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

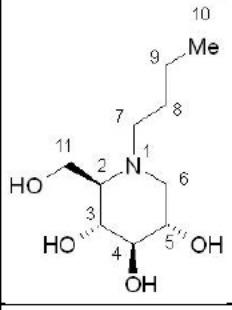
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules	**Adequate**
Strength(s) in metric system	65 mg	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	capsule size, color and imprinting are provided	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	**Not Adequate** Change to: OPFOLDA (miglustat) capsules
Dosage form(s) and route(s) of administration	capsules	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	**Adequate**
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	**Adequate**
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	enzyme stabilizer	**Adequate**

Chemical name, structural formula, molecular weight	Molecular weight: 219.28 g/mol Molecular formula: $C_{10}H_{21}NO_4$ Chemical name: 1,5-(butylimino)-1,5-dideoxy-D-glucitol Chemical structure:  	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Miglustat is a white to off white crystalline solid (powder). It is highly soluble in water (> 1000 mg/mL as a free base).	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

(b) (4)

(b) (4)	NDC
4 count bottle	71904-300-01
24 count bottle	71904-300-02
100 count bottle	71904-300-03

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F), [See USP Controlled Room Temperature].

(b) (4)

Store in the original container (b) (4) to protect from light.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	capsules	**Adequate**
Strength(s) in metric system	65 mg	**Adequate**
Available units (e.g., bottles of 100 tablets)	4 count, 24 count, 100 count	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	hard gelatin capsule NDC numbers provided	**Not Adequate** Add "size 2, hard gelatin capsule with a white opaque body and gray opaque cap printed with "AT2221"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) Store in the original container (b) (4) to protect from light.	**Adequate**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F), [See USP Controlled Room Temperature].	**Adequate**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	

Include information about child-resistant packaging	not provided	**Not Adequate** **Add "bottle with child resistant closure"**

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Amicus Therapeutics US, LLC 3675 Market Street Philadelphia, PA 19104	**Adequate**

2.0 PATIENT LABELING

The following CMC information provided in the Patient Information is adequate

How should I store OPFOLDA?

- Store OPFOLDA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep OPFOLDA capsules in the original container or equivalent to protect from light.

Keep OPFOLDA and all medicines out of the reach of children.

What are the ingredients in OPFOLDA?

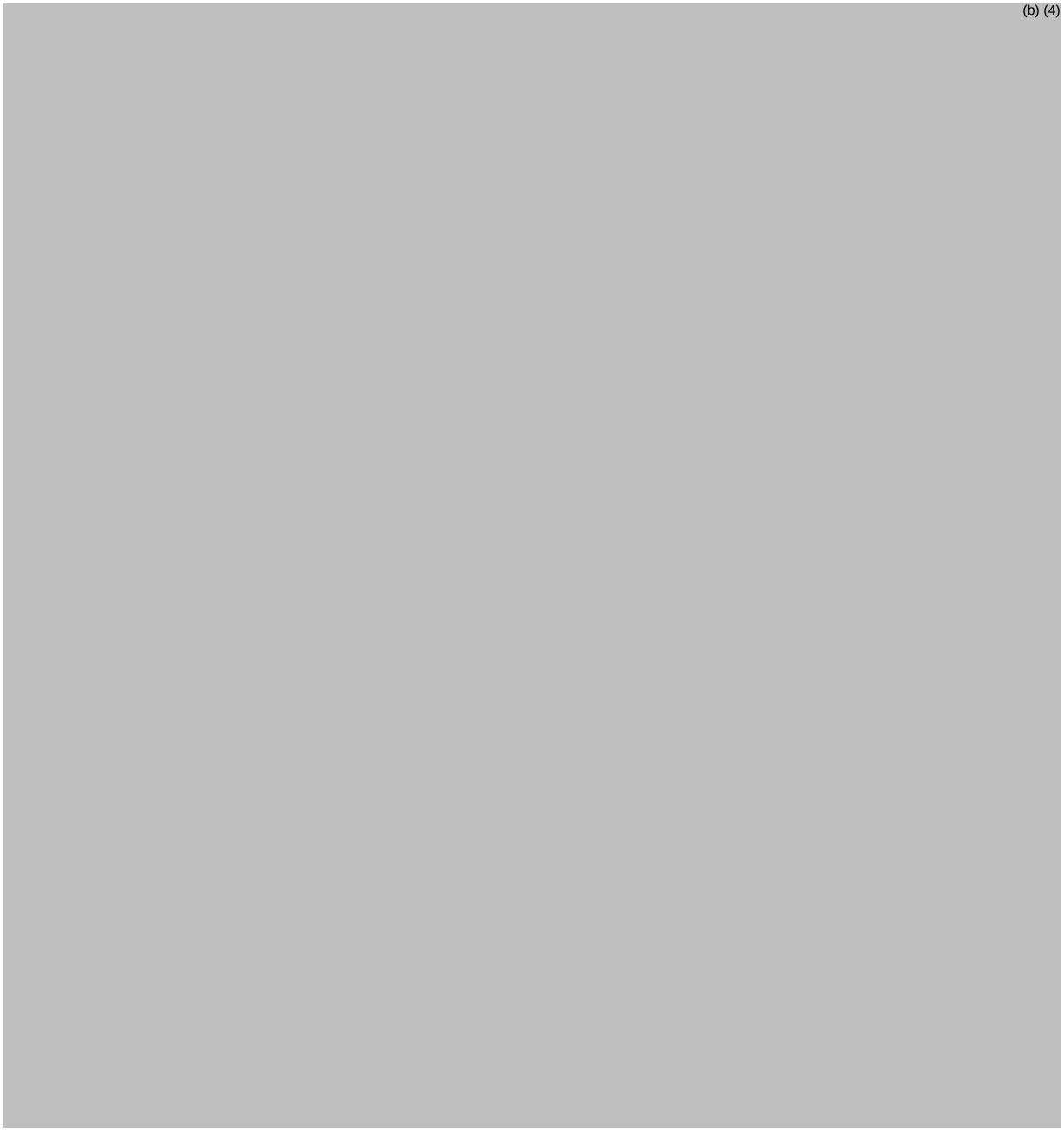
Active ingredient: miglustat

(b) (4)

Manufactured for:
Amicus Therapeutics US, LLC
3675 Market Street
Philadelphia, PA 19104 USA

3.0 CARTON AND CONTAINER LABELING

3.1 Bottle Label



3.2 Carton Labeling

None

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	OPFOLDA (migLUstat) capsules	**Not Adequate** - Change established name to all lowercase "miglustat" throughout the labeling
Dosage strength	65 mg	**Adequate**
Route of administration	oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	100, 24, 4 capsules	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Provided	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	**Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	**Adequate**
Medication Guide (if applicable)		**Adequate**
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	(b) (4)	**Adequate**

Assessment of Carton and Container Labeling: *Inadequate*

1. Make the following editorial change in the prescribing information during the team labeling review:
    - Remove comma between establish name and dosage form in the Highlight section
    - Change (b) (4) to OPFOLDA (miglustat) capsules in section 11
    - Add "size 2, hard gelatin capsule with a white opaque body and gray opaque cap printed with "AT2221" in section 16
    - Add "bottle with child resistant closure" in section 16

2. The following deficiencies in the container labels need to be conveyed to the applicant:
    - Change established name to all lowercase "miglustat" throughout the container labels

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

The following deficiencies in the carton/container labels need to be conveyed to the applicant

- Change established name to all lowercase "miglustat" throughout the container labels

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Hong Cai, Ph. D.
Branch Chief, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 1/05/2022 09:25:50AM
GUID: 508da7210002a030e76df4f60ccd142a

Hong Cai

Digitally signed by Hong Cai
Date: 1/05/2022 09:52:51AM
GUID: 55919d6500e16bdaad5825645e4f22ff

Memorandum

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

Date: **March 21, 2022**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Hong Cai, Ph.D.**
Chief, ONDP/Division II/Branch IV

To: **Labeling Review #1 of NDA 215211**

Subject: **Final labeling/labels**

The Labeling review #1 has noted the following pending issues: 1) Minor editorial changes to the Prescribing Information to be made during the NDA team labeling review; 2) Change established name to all lowercase "miglustat" throughout the container labels.

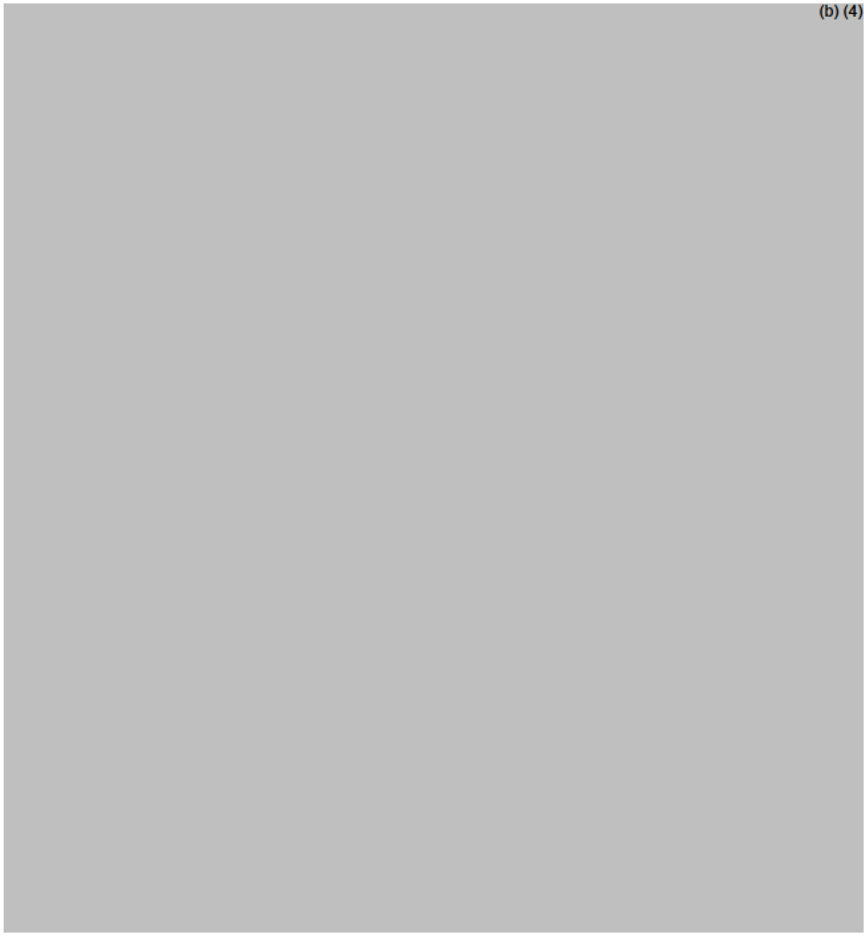
The editorial changes have been implemented in the prescribing information. However, the upper cases of "migLUstat" on the container labels have been retained to follow "FDA List of Established Drug Names Recommended to Use Tall Man Lettering (TML)" to help differentiate look-alike drug names dated 28-Apr-2020 (https://www.fda.gov/drugs/medication-errors-related-cder-regulated-drug-products/fda-name-differentiation-project). The revised container labels provided in the **Attachment** are satisfactory from ONDP perspective.

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

Attachment:

Bottle Labels:



Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 4/18/2022 04:19:10PM
GUID: 508da7210002a030e76df4f60ccd142a

Hong Cai

Digitally signed by Hong Cai
Date: 4/18/2022 08:58:53PM
GUID: 55919d6500e16bdaad5825645e4f22ff

26 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

QUALITY REVIEW

BIOPHARMACUTICS
NDA: NDA 215211
Drug Product Name / Strength: Opfolda (Miglustat, 65 mg) Capsule
Route of Administration: Oral
Applicant Name: Amicus Therapeutics US, LLC
Indication: Treatment of Pompe disease
Submission date: 07/29/2022
Primary Reviewer: Kamrun Nahar, Ph.D.
Secondary Reviewer: Vidula Kolhatkar, Ph.D.
Recommendation: Adequate

BACKGROUND:
The Applicant is seeking approval under 505(b)(1) regulatory pathways for Opfolda (Miglustat, 65 mg) Capsule, for oral administration, indicated for the treatment of Pompe disease.

REVIEW SUMMARY:
The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data:

1) **Dissolution Method and Acceptance Criteria:**
The Applicant used in-house dissolution method for the Miglustat capsule which is as follows- USP apparatus II (paddle), 75 rpm, 500 mL of 0.01N HCl at 37°C. The Applicant's proposed a dissolution acceptance criterion of "Q (b)(4)% in 15 minutes" as quality control for batch release and stability testing of the proposed drug product. The dissolution method does not have discriminating ability. Considering high solubility of Miglustat this is acceptable.

The approved dissolution method and acceptance criterion for quality control and stability testing of the proposed Opfolda (Miglustat, 65 mg) Capsule:

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	75	0.01N HCl	500	37±0.5°C	Q= (b)(4)% in 15 minutes

2) **Bridging of Formulations:**
The Applicant tested one strength of the proposed product Miglustat capsules, 65 mg. The Applicant used three formulations during the development of the Miglustat capsules, 65mg. First, they have used Miglustat (b)(4) in phase 1/2 study. To enable scale up and to support on going phase 1/2 and phase 3 clinical trials and for commercial supplies, a new capsule formulation was developed. The new capsule formulation (b)(4) (b)(4) in hard gelatin capsule shells (white body/ (b)(4) cap). Finally, to finalize commercial formulation, the Applicant further changed the color of the capsule's shells (white body/gray cap) and printing on it. The Applicant bridged the phase

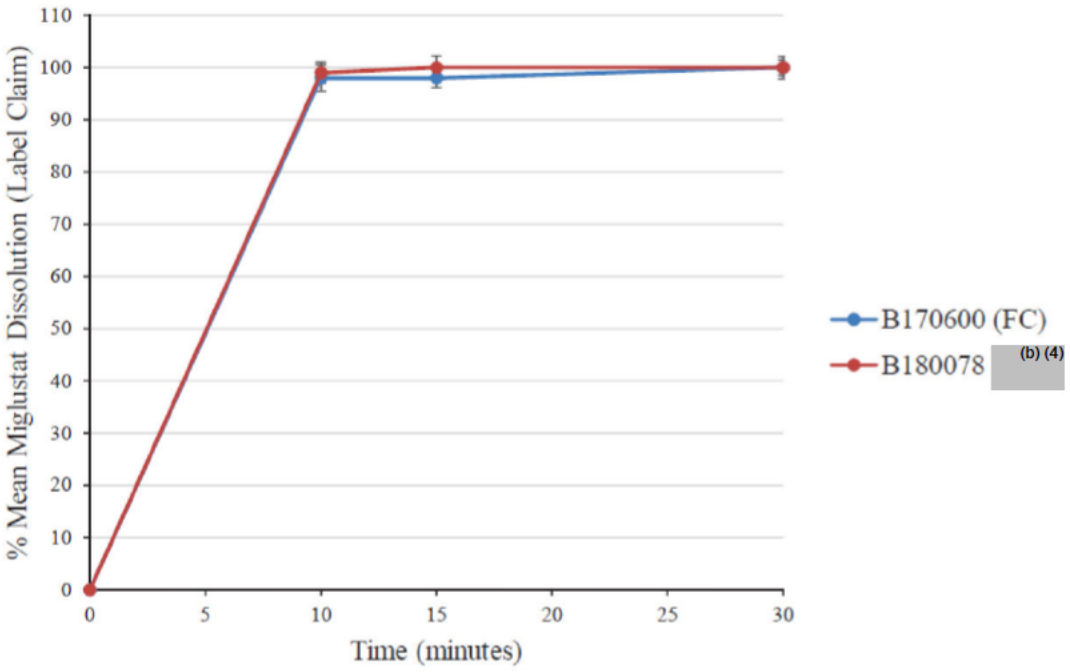
1/2 (b) (4) and phase 3 formulation (Miglustat capsules, 65mg, (b) (4) cap/white body) through bioequivalence study (AT2221-01) and dissolution test. Bioequivalence study will be assessed by Clinical Pharmacology team. The Applicant conducted comparative dissolution tests (Figure 1) of the phase 3 and commercial formulation to bridge the changes in capsule shell. Dissolution test showed similar drug release from the (b) (4) and commercial formulations.

Table 1: Formulation development summary for Miglustat capsules, 65 mg

	Formulation Development During Phase 1/2/3			Proposed Commercial
Clinical phase	1/2	1/2, 3	3	
Use	Bioavailability/ Clinical/Stability/ Dissolution Study	Bioavailability/ Clinical/Stability/ Dissolution Study	Clinical/Primary Stability/ Dissolution Study	
Drug substance manufacturer	(b) (4)			(b) (4)
Formulation		Commercial Formulation		
Component	Quantity (mg per capsule)			
Miglustat	65.0	65.0	65.0	65.0
Microcrystalline cellulose	(b) (4)			(b) (4)
Starch, pregelatinized maize				
Sucralose				
Magnesium stearate				
Colloidal silicon dioxide				
Capsule size	2	2	2	2
Capsule color	(b) (4) Opaque cap / White Opaque body	(b) (4) Opaque cap / White Opaque body	Gray Opaque cap / White Opaque body	Gray Opaque cap / White Opaque body
Capsule printing	(b) (4)		"AT2221" printed in black ink on body	"AT2221" printed in black ink on body

Abbreviations: (b) (4)

Figure 1: Dissolution comparison study between (b) (4) ((b) (4) batch# B180078) and commercial formulation (commercial formulation, (b) (4) cap/white body, batch# B170600)



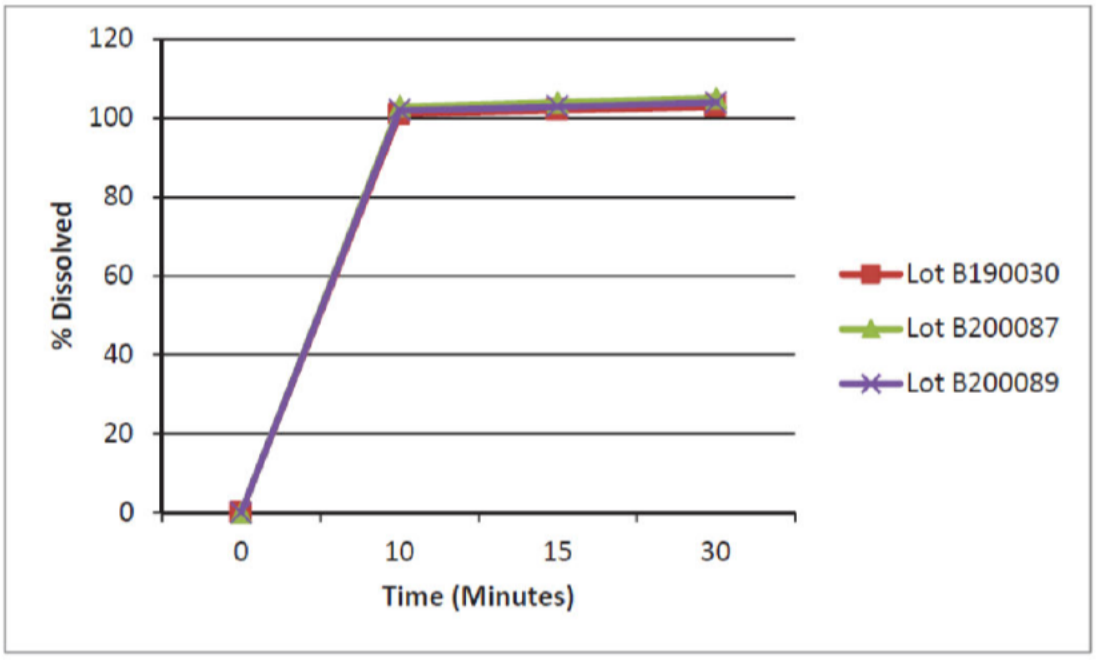
Abbreviation: FC = formulated capsules (commercial formulation) (b) (4)

During, phase 3 clinical trials, there were changes to capsule shells (b) (4) (b) (4) The Applicant used two API sources (b) (4) for both Phase 3 and commercial product. The capsule composition was same for the Phase 3 and commercial batches. To compare the drug release from the drug products due to changes in the capsule shells and drug substance sources a comparative dissolution study was performed using the QC dissolution method. Based on the dissolution profile of the formulations with different capsule shell color and drug substance sources (figure 2), drug release from the capsules was not affected due to the differences in shells color and drug substance sources.

Table 2: Batch information for dissolution comparison study

Bulk Product Batch Number	B190030	B200087	B200089
Packaged Product Batch Number	B190167	B200120	B200124
Dosage Strength	65 mg		
Site of Manufacture	(b) (4)		
Date of Manufacture	28 Jan 2019	23 Mar 2020	26 Mar 2020
Batch Size	(b) (4)		
Drug Substance Manufacturer			
Studies Used In	Clinical/Stability	Clinical/Primary Stability	Primary Stability
Capsule Shell	(b) (4) Opaque cap / White Opaque body	White opaque body and gray opaque cap, "AT2221" printed on the body in black ink	White opaque body and gray opaque cap, "AT2221" printed on the body in black ink

Figure 2: Dissolution profiles for Miglustat capsules, 65 mg batches# B190030 (white opaque capsule body and DS source: (b) (4)); B200087 (white opaque capsule body and gray opaque cap with black printing, DS source: (b) (4)); and B200089 (white opaque capsule body and gray opaque cap with black printing, DS source: (b) (4) (b) (4))



Note: Lot B190030 = white opaque (b) (4) body; (b) (4)
Lot B200087 = White opaque body and gray opaque capsule with black printing;
Lot B200089 = White opaque body and gray opaque capsule with black printing; (b) (4)

3) **Biowaiver:**
Not applicable. The proposed product has only one strength, thus no biowaiver is needed or was requested.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 215211 Opfolda (Miglustat, 65 mg) Capsule is **adequate**.

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed:

1. 0001 07/29/2021 Original submission
2. 0007 11/05/2021 Response to FDA Quality Information Request

Highlight Key Outstanding Issues from Last Cycle: None

I. Solubility Per Biopharmaceutical Classification System (BCS):

The Applicant claimed that Miglustat is a highly soluble compound. The solubility data of Miglustat showed that the drug is highly soluble across the physiological pH range (b) (4) in aqueous media.

Table 3: Miglustat solubility data

Buffer Solution	pH of Buffer Solution	Solubility
(b) (4)	(b) (4)	> 200 mg/mL
Succinate, 0.2M buffer solution		> 200 mg/mL
Phosphate, 0.2M buffer solution		> 200 mg/mL

II. Dosage Form:

The proposed drug product, Miglustat capsules, 65 mg, is an immediate release capsule for oral administration. Miglustat capsule is a size 2, hard gelatin capsule with a white opaque body and gray opaque cap containing white to off-white powder. "AT2221" is printed in black ink on the white opaque body.

Table 4: Components of the Miglustat capsules, 65 mg

Component	Quality Standard	Function	Quantity per Capsule (mg)	Percent by Weight (%)
Miglustat	In-house	Active	65.0	(b) (4)
Microcrystalline cellulose	Ph. Eur., USP/NF, and JP			(b) (4)
Starch, pregelatinized maize	Ph. Eur., USP/NF, and JPE			
Sucralose	Ph. Eur., USP/NF, and JPE			
Magnesium stearate	Ph. Eur., USP/NF, and JP			
Colloidal silicon dioxide	Ph. Eur., USP/NF, and JP			
(b) (4)				
Hard gelation capsule, size 2	JP			
Total	-			

Abbreviations: JP = Japanese Pharmacopoeia; JPE = Japanese Pharmaceutical Excipients; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia

(b) (4)

III. Dissolution Method:

Miglustat is highly soluble across the physiological pH range (b) (4) The Applicant chose 500 mL of 0.01N HCl as the dissolution media. The Applicant stated that at the beginning, dissolution was conducted using USP apparatus II, (b) (4) rpm, in 500 mL of 0.01N HCl at 37±0.5°C using (b) (4) formulation. Dissolution apparatus rotation speed (rpm) was further modified to 75 rpm (b) (4) Although the Applicant mentioned that they have modified dissolution apparatus speed to 75 rpm (b) (4) they did not provide detail information regarding this issue. The Applicant performed dissolution test (b) (4)

(b) (4)

(b) (4).

Although the Applicant selected 0.01N HCl as the QC dissolution media, they did not justify the reason for that. (b) (4)

(b) (4)

Therefore, selection of 0.01N HCl as the dissolution is deemed adequate. The Applicant did not investigate the discriminating ability of the dissolution method. Moreover, dissolution data showed very rapid drug release, i.e., > (b) (4) % in 15 minutes in all the tested media, indicating that dissolution method lacks discriminating ability.

In conclusion, the drug substance is a highly soluble compound, dissolution data showed very rapid release of the drug with low variability and dissolution method lacks discriminating ability to the variations in formulation, capsule shell differences and drug substance sources. Based on the totality of the information, dissolution method is deemed adequate.

Dissolution acceptance criterion:

Approved dissolution method and acceptance criterion of Miglustat capsules, 65mg

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	75	0.01N HCl	500	37±0.5°C	Q= (b)(4)% in 15 minutes

Dissolution Acceptance Criterion:

The Applicant proposed dissolution acceptance criterion as "Q= (b)(4)% in 15 minutes". Dissolution data of the clinical batches in the proposed QC dissolution method showed that > (b)(4)% drug is released in 15 minutes. Therefore, based on the dissolution data, the proposed dissolution acceptance criterion "Q= (b)(4)% in 15 minutes" is adequate.

Table 6. Dissolution profile data of Miglustat capsules, 65 mg (batches# B190167 ((b)(4) cap/white body; (b)(4) clinical/ stability) and B200120 (white body/gray cap, AT2221 print on the body; (b)(4) clinical/ stability) is the clinical/ stability batches; batch# B200124 (white body/gray cap, AT2221 print on the body; (b)(4) primary stability batch)

Batch #	B190167			B200120			B200124		
Vessel	Date of test: 16 Jul 2020			Date of test: 17 Jul 2020			Date of test: 17 Jul 2020		
	Miglustat Dissolved (%)			Miglustat Dissolved (%)			Miglustat Dissolved (%)		
	10 Minutes	15 Minutes	30 Minutes	10 Minutes	15 Minutes	30 Minutes	10 Minutes	15 Minutes	30 Minutes
1	(b)(4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	101	102	103	103	104	105	102	103	104
% RSD	2.3	2.0	1.8	2.5	2.1	1.9	2.5	2.1	1.8

Appendix 1. Dissolution Data

Dissolution data: \\CDSESUB1\evsprod\nda215211\0001\m3\32-body-data\32p-drug-prod\miglustat-65mgcapsule-(b) (4)32p2-pharm-dev\pharmaceutical-development-drugprod.pdf

Appendix 2. Information Request and Responses

Information Request (10/25/2021):
Provide the solubility data of Miglustat across the physiological pH range (b) (4) in aqueous media.

Applicant's Response (11/05/2021): \\CDSESUB1\evsprod\nda215211\0007\m1\us\111-info-amend\quality-info-amend.pdf

Reviewer's assessment: The Applicant provided solubility data of the Miglustat capsules across the physiological pH range (b) (4) in aqueous media. The solubility table is provided in the current review. The response is adequate.

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 2/15/2022 10:27:06AM
GUID: 5424aeae00c3274f93e50573f7ca407e

Kamrun Nahar

Digitally signed by Kamrun Nahar
Date: 2/14/2022 05:12:05PM
GUID: 57b38236009c032e2a84627cd295a5cd

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
05/18/2022 11:25:05 AM