CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208623Orig1s000

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: **August 3, 2018**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 208623**

Subject: Final Recommendation for NDA 208623

At the time when the CMC Review #1 was completed on June 12, 2018 it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised immediate container (inner sleeve)/carton (outer sleeve) labels and Prescribing Information (PI) on July 19, and July 30, 2018, respectively, and the submitted CMC sections of the labeling/labels were reviewed and found acceptable. (**See the Attachment)**

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V Division of New Drug Products II
August 3, 2018

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2018.08.03 15:21:16 -04'00'

Attachment:

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

DATE: **August 2, 2018**

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: **Prescribing Information (PI), Immediate Container, and Carton Labeling/Label review # 1 for NDA 208623**

SUBJECT: **Final ONDP Recommendation from the Labeling/Label Review Perspective**

In the review #1 of NDA 208623, the application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling as well as immediate container (blister) and carton labels.

The CMC labeling-label deficiencies identified during the review # 1 of NDA 208623 on May 1, 2018 were conveyed to the applicant (see the **Attachment**).

The applicant has submitted the revised immediate container (inner sleeve)/carton (outer sleeve) labels and Prescribing Information (PI) on July 19, and July 30, 2018, respectively

A. PI

a) Highlight Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GALAFOLD safely and effectively. See full prescribing information for GALAFOLD.

GALAFOLD™ (migalastat) capsules, for oral use
Initial U.S. Approval: 2018

DOSAGE FORMS AND STRENGTHS
Capsules: 123 mg migalastat. (3)

Evaluation: Based on the new labeling guidance the equivalent statement for the active moiety is only to be provided in section 11 of the PI, "Description".

Conclusion: *The* ***Highlight Section*** *of the PI is now considered* ***satisfactory****.*

b) Full Prescribing Information

#3: Dosage Forms and Strengths

Capsules: 123 mg of migalastat in a size "2" capsule with an opaque blue cap and opaque white body with "A1001" printed in black, containing white to pale brown powder.

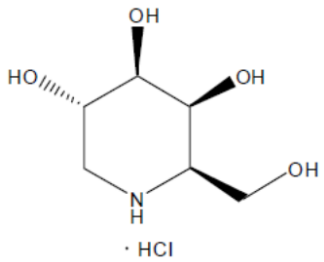
Evaluation: Based on the new labeling guidance the equivalent statement for the active moiety is only to be provided in section 11 of the PI, "Description".

Conclusion: *The revised* ***Dosage Form*** *and* ***Strengths*** *section of the* ***Full Prescribing Information*** *of the PI are now considered* ***satisfactory****.*

#11: Description

GALAFOLD (migalastat), an alpha-Galactosidase A (alpha-Gal A) pharmacological chaperone, contains migalastat hydrochloride as the active ingredient, a low molecular weight iminosugar and an analogue of the terminal galactose of globotriaosylceramide (GL-3).

The chemical name for migalastat hydrochloride is (+)-(2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl) piperidine-3,4,5-triol hydrochloride. Its molecular formula is $C_6H_{13}NO_4$•HCl, molecular mass is 199.63 g/mol, and its chemical structure is depicted below.



Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble in aqueous media within the pH range of 1.2 to 7.5.

GALAFOLD (migalastat) capsules for oral administration contain 123 mg of migalastat (equivalent to 150 mg migalastat hydrochloride) as a white to pale brown powder and are supplied in a size "2" hard gelatin capsule with an opaque blue cap and an opaque white body imprinted with "A1001" in black

ink. The inactive ingredients are magnesium stearate and pregelatinized starch. Capsule shells consist of gelatin, indigotine-FD&C Blue 2, and titanium dioxide. The black ink consists of black iron oxide, potassium hydroxide, and shellac.

Evaluation: The established name and chemical name for the active moiety as well as the pharmacological class have been added to this section.

Conclusion: *The revised* ***Description*** *section of the* ***Full Prescribing Information*** *of the PI is now considered* ***satisfactory****.*

#16: How Supplied/Storage and Handling

16.1 How Supplied

GALAFOLD capsules are supplied as 123 mg migalastat, size "2" capsules with opaque blue cap and opaque white body filled with white to pale brown powder and imprinted with "A1001" in black ink.

GALAFOLD capsules are packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks (28 days).

Wallet pack containing 14 GALAFOLD capsules NDC 72904-100-01.

Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

Evaluation: Based on the new labeling guidance the equivalent statement for the active moiety is only to be provided in section 11 of the PI, "Description". A concise description/identification of the dosage form has been added to this section of PI.

Conclusion: *The revised* ***How Supplied/storage*** *and* ***Handling*** *section of the* ***Full Prescribing Information*** *of the PI is now considered* ***satisfactory****.*

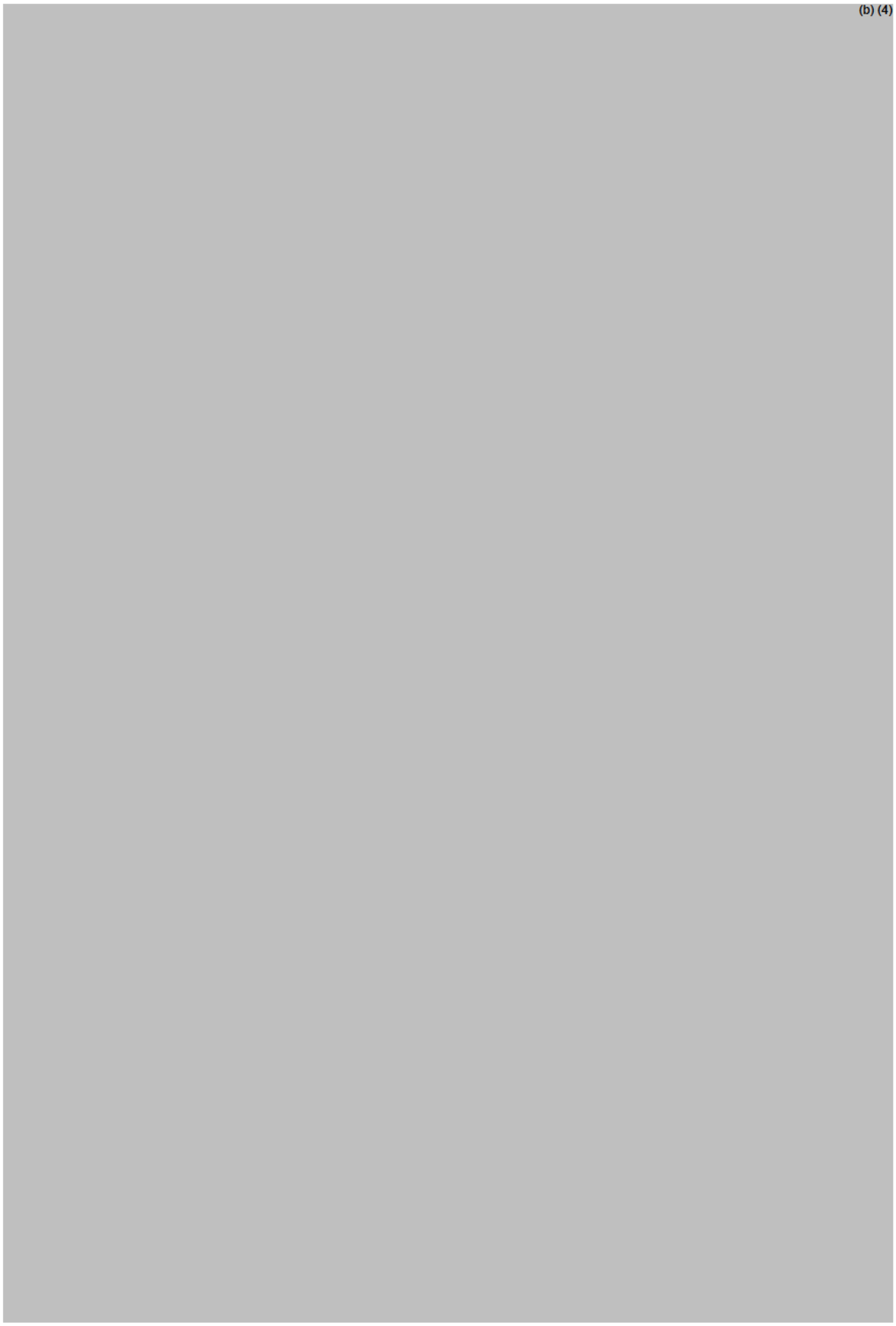
Container/Carton Labels:

a. Immediate container labels: Inner sleeve

Evaluation: Net content, Rx only, NDC number, barcode, storage conditions, lot number and expiration date have been added to the inner sleeve.

Conclusion: *The revised* ***Inner Sleeve*** *is now considered* ***Satisfactory****.*

b. Carton labels: Outer sleeve



Evaluation: NDC number has been added to the outer sleeve.

Conclusion: *The revised* ***Outer Sleeve*** *is now considered* ***Satisfactory****.*

Recommendation: This application now considered ready for **approval** from the PI, immediate container, and carton labeling-label perspective.

Attachment: The deficiencies previously noted in the Review #1 and conveyed to the applicant via the CR letter on May 1, 2018

A. Regarding PI

Highlights:

Revise "Dosage Forms and Strengths" from "Capsules: 123 mg of migalastat" to (b) (4)

Full Prescribing Information

#3: Dosage Forms and Strengths

Dosage Form and Strengths" section must be revised to include:

(b) (4)

The following revisions is recommended:

(b) (4)

#11: Description

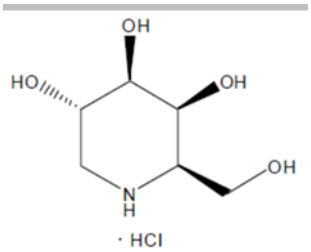
"Description" section must be revised to include:

1) Established name for the active moiety
2) The chemical name for the active ingredient
3) The proper pharmacological class.

The following revision is suggested:

(b) (4)

(b) (4)



Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble in aqueous media within the pH range of 1.2 to 7.5.

(b) (4)

#16: How Supplied/Storage and Handling

"How Supplied/Storage and Handling" section must be revised to include:

(b) (4)

2) A concise description/identification of the dosage form. The

The following revision is recommended:

(b) (4)

Galafold capsules are packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks (28 days).

Wallet pack containing 14 Galafold capsules NDC XXXXX-YYYY-ZZ (the actual NDC number must be provided)

Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

B. Regarding of the Container/Carton Labels:

a) Blister card inner sleeve label:

Revise the blister card inner sleeve labels to address the following:

1) Display net content (14 capsules)
2) Display Rx only
3) Display the actual NDC number.
4) Display lot number and expiration date
5) Display bar code
6) Display storage conditions

b) Blister card outer sleeve label:

Add the actual NDC number to the blister card outer sleeve

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 8/03/2018 01:12:15PM
GUID: 502d0913000029f9798ca689a802fa55

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 8/03/2018 11:21:47AM
GUID: 507d824300005f344cf8b5e5989f0057

QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(1) NDA is not ready for Approval in its present form per 21 CFR 314.125(b)(6)

NDA 208623
Review #1

Drug Name/Dosage Form	Galafold (migalastat) capsules
Strength	123 mg migalastat equivalent to 150 migalastat hydrochloride salt
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Amicus Therapeutics U.S., Inc.; Cranbury, NJ
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	12/13/2017	OPQ
Amendment	2/16/2018	OPQ/ONDP/NDAPI, ONDP/DB/BBII and OPF
Amendment	3/12/2018	ONDP/DB/BBII
Amendment	4/6/18	ONDP/DB/BBII
Amendment	4/10/2018	ONDP/DB/BBII
Amendment	4/17/2018	ONDP
Amendment	5/11/2018	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Environmental Analysis (EA)	Hamid R. Shafiei	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process and Microbiology	Tianhong Tim Zhao	CDER/OPQ/OPF/ DPAIII/PABVIII
Biopharmaceutics	Jae Wook Yoo	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Facilities	Vidya Pai	OMPT/CDER/OPQ/OPF /DIA/IABIII
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		Active	N/A	LOA October 18, 2017
	Type III			Active	N/A	September 27, 2017

N/A: There is enough data in the application, therefore, the DMF did not need to be reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68456	Treatment for Fabry disease, Amicus Therapeutics US, Inc., June 21, 2004

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the issues regarding label/labeling have ***not*** been completely resolved yet as of this review. (see the **List of Deficiencies**)

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per 21 CFR 314.125(b)(6) until the label/labeling issues are satisfactorily resolved.

II. Summary of Quality Assessments

A. Product Overview

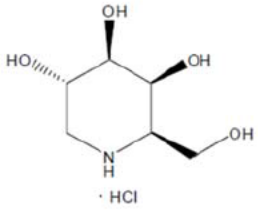
Migalastat capsule is indicated for the treatment of patients with Fabry disease with amenable mutations. The size 2 hard gelatin capsules are supplied in 123 mg strength. Each capsule contains 123 mg migalastat equivalent to 150 mg of migalastat hydrochloride salt. Each blister pack contains 14 capsules for one month supply. Migalastat has never been approved in US, however, it is approved in EU in 2016 as Galafold capsules for the same indication.

Proposed Indication(s) including Intended Patient Population	For the treatment of patients (b) (4) with Fabry disease and who have an amenable mutation.
Duration of Treatment	As long as needed
Maximum Daily Dose	Recommended dose is 123 mg once every other day taken orally
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The drug substance in Galafold capsules is migalastat hydrochloride. It is a chiral iminosugar with 4 asymmetric centers synthesized as a single enantiomer as proven by single crystal X-ray crystallography. It is a low molecular weight compound with the chemical name of (+)-(2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl) piperidine-3,4,5-triol, hydrochloride. Its molecular formula is $C_{16}H_{13}NO_4$.HCl with molecular weight of 199.63. It is a white to almost white solid, freely soluble in water but very slightly soluble in alcohol. It is produced in only one chiral and polymorphic Form 1. It is non-hygroscopic. It is a Biopharmaceutical Classification System (BCS) Class III compound with high solubility across the physiological range and between pH 1.2 to pH 7.5 and low passive permeability.



Migalastat Hydrochloride

Migalastat hydrochloride is manufactured by [redacted]. The detailed information regarding the drug substance manufacturing process, in-process controls, control of materials, control of critical steps and intermediates was provided. The chemical structure of migalastat hydrochloride was confirmed by elemental analysis, proton (^{1}H) and carbon (^{13}C) NMR spectroscopy; mass spectroscopy, IR spectroscopy, optical rotation and single crystal X-ray crystallography.

The quality of the drug substance, migalastat hydrochloride, is controlled by its specification which includes identity by IR, HPLC and chloride test; assay by HPLC, impurities by HPLC, residual solvents by GC, [redacted] by ICP-MS. Satisfactory batch analyses of the drug substance batches used in the nonclinical, clinical and stability studies were provided.

The bulk drug substance is stored [redacted]. On the basis of satisfactory results of long-term and acclerated stability testing a retest period of [redacted] months was granted when stored at [redacted] in the proposed container closure system.

The CMC information regarding the drug substance, migalastat hydrochloride, was reviewed by the drug substance reviewer, Dr. Joseph Leginus, and concluded that sufficient information is provided to ensure consistent manufacturing of migalastat hydrochloride with respect to identity; strength, purity and quality (see the **Drug Substance** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Vidya Pai, has made an "Adequate" recommendation for the drug substance manufacturing and testing facility (see the **Facilities** review).

Migalastat hydrochloride is manufactured and controlled per the manufacturing process described in Sec. 3.2.S.2 (b) (4) (b) (4) and conforms to the requirements (specification) for drug product formulation of Migalastat capsules.

Drug Product:
Migalastat capsules are indicated for the treatment of patients with Fabry disease with amenable mutations. Migalastat capsule is size "2" hard gelatin capsule with an opaque blue cap and an opaque white body, printed with the identifying code "A1001", containing white to pale brown powder. Each capsule contains 123 mg migalastat equivalent to 150 mg migalastat hydrochloride and the following inactive ingredients: pregelatinized (b) (4) starch and magnesium stearate. The capsules are packed in (b) (4) (b) (4) blister packs with aluminum foil lidding. Each blister pack contains 14 capsules as one month supply.

Migalastat capsules are manufactured by (b) (4) (b) (4) (b) (4) There is no overage of any ingredients in the drug product formulation. (b) (4) The registration and commercial scale batches are (b) (4) capsules each. The drug product manufacturing process and microbiology assessment were reviewed by Dr. Tianhong Tim Zhou and were found to be acceptable (see the **Process** review).

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, uniformity of dosage units, dissolution, and microbial purity.

Based on satisfactory long-term and accelerated stability testing results of the drug product assuring the identity, strength, purity, and quality, the proposed **48-month of expiration dating period** is granted when stored at room temperature in the proposed container closure system per drug product reviewer, Dr. Hamid Shafiei (see the **Drug Product** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Vidya Pai, has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (see the **Facility** review).

The applicant submitted a claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b) and a statement of no extraordinary circumstances existed was

included. The claim was reviewed and found to be acceptable.

The drug product dissolution methods development, dissolution data and dissolution specification were reviewed by Dr. Jae Wook Yoo and deemed adequate from biopharmaceutical perspective. (see the **Biopharmaceutics** review)

The proposed labels and labeling are under review and they are not deemed adequate from the CMC perspective per Dr. Hamid Shafiei (see **Labeling** review) because the labels and labeling issues have not been completely resolved as of this review (see the **List of Deficiencies**).

C. Lifecycle Management Consideration (NDA only)

None

D. Special Product Quality Labeling Recommendations (NDA only)

None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies:

The following labeling comments should be resolved with the applicant.

A. <u>Regarding PI</u>

Highlights:

Revise "Dosage Forms and Strengths" from "Capsules: 123 mg of migalastat" to (b) (4)

Full Prescribing Information:

#3: Dosage Forms and Strengths

Dosage Form and Strengths" section should be revised to include:

(b) (4)

With the following suggested revision:

(b) (4)

#11: Description

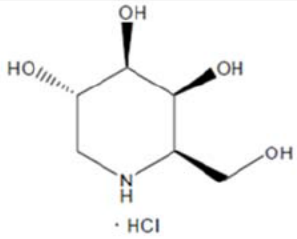
"Description" section should be revised to include:

1) Established name with the active moiety
2) The chemical name for the active ingredient
3) The proper pharmacological class.

With the following suggested revision:

(b) (4)

(b) (4)



Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble in aqueous media within the pH range of 1.2 to 7.5.

(b) (4)

#16: How Supplied/Storage and Handling

"How Supplied/Storage and Handling" section should be revised to include:

(b) (4)

2) A concise description/identification of the dosage form.

With the following suggested revision:

(b) (4)

Galafold capsules are packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks (28 days).
Wallet pack containing 14 Galafold capsules NDC XXXXX-YYYY-ZZ (the actual NDC number must be provided)
Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F)."

B. Regarding of the Container/Carton Labels:

a) Blister card inner sleeve label:
Revise the blister card inner sleeve labels to address the following:

1) Display net content (14 capsules)
2) Display Rx only
3) Display the actual NDC number.
4) Display lot number and expiration date
5) Display bar code
6) Display storage conditions

b) Blister card outer sleeve label:
Add the actual NDC number to the blister card outer sleeve

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
June 12, 2018

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2018.06.12 20:36:40 -04'00'

100 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background

Application: NDA 208623; New Molecular Entity (NME); Orphan Drug designation (Rare Disease)

Drug Product Name / Strength: Galafold™ (Migalastat hydrochloride) Capsule/150 mg (Migalastat 123mg free base capsule)

Indication: For use in patients with Fabry disease who have an amenable mutation in the GLA gene.

Route of Administration: Oral

Applicant Name: Amicus Therapeutics US Inc.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

The proposed drug product, Galafold™ (Migalastat Hydrochloride) is an immediate release hard gelatin capsule indicated for use in patients with Fabry disease who have an amenable mutation in the GLA gene. The NDA 208623 application for this drug product was submitted on 12/13/17 under 505(b)(1) by Amicus Therapeutics US Inc. The proposed dose strength is Migalastat 123mg (free base equivalent to Migalastat Hydrochloride 150mg) capsule and recommended to be administered orally once every other day.

The focus of Biopharmaceutics review is on the dissolution method development, dissolution data, and dissolution specification. Based on a thorough review, NDA 208623 for Galafold™ (Migalastat 123mg) capsule is adequate from the Biopharmaceutics perspective.

Proposed dissolution specification by the applicant: Not less than (b)(4)% (Q) Migalastat released at 15 minutes

List Submissions being reviewed (table):

Received Date	Submission
12/13/2017	Application 208623 - Sequence 0001 - 0001 (1) 12/13/2017 ORIG-1 /Multiple Categories/Subcategories
2/16/2018	Application 208623 - Sequence 0006 - 0006 (6) 02/16/2018 ORIG-1 /Quality/Response To Information Request
3/12/2018	Application 208623 - Sequence 0010 - 0010 (10) 03/12/2018 ORIG-1 /Quality/Response To Information Request
4/6/2018	Application 208623 - Sequence 0015 - 0015 (15) 04/06/2018 ORIG-1 /Quality/Response To Information Request
4/10/2018	Application 208623 - Sequence 0016 - 0016 (16) 04/10/2018 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: This is the original review cycle.

Concise Description Outstanding Issues Remaining: N/A

List Number of Comparability Protocols (ANDA only): N/A

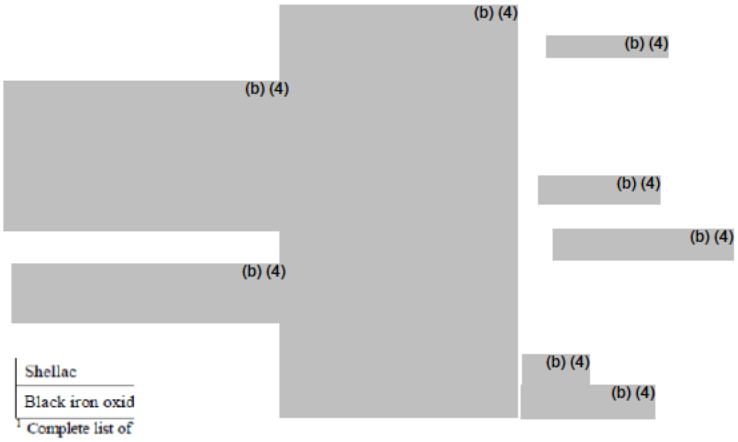
A. Summary of Drug Product Composition and Development

The components and quantitative composition of Migalastat capsule 123mg is shown in Table 1. The composition of a hard gelatin capsule is shown in Table 2.

Table 1: Composition of Migalastat Capsule 123mg

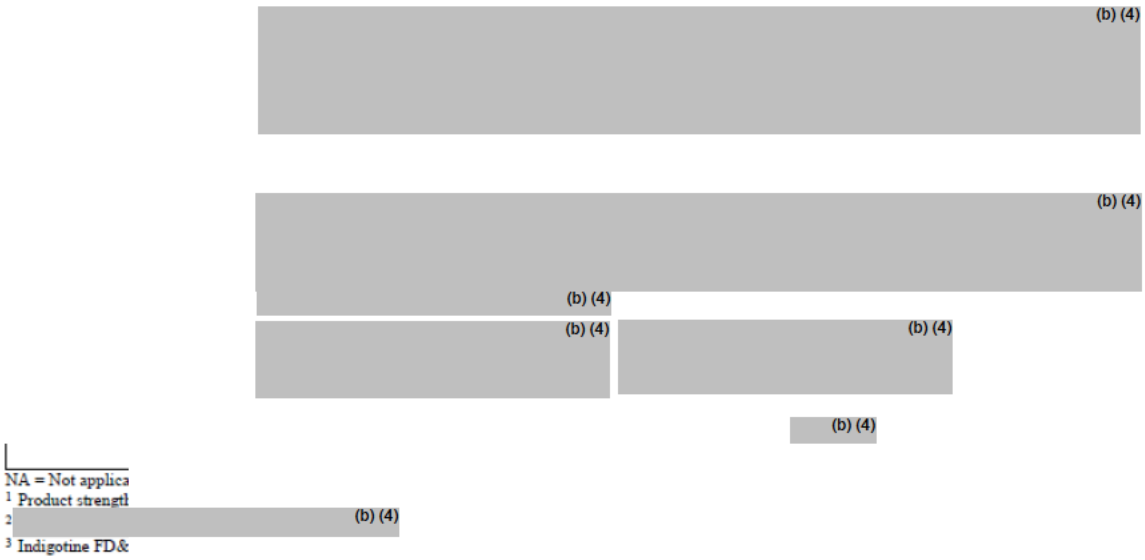
(b) (4) (b) (4) (b) (4) migalastat fi [2] Migalastat h accompanie (b) (4) (b) (4) (b) (4)

Table 2: Composition of Hard Gelatin Capsule



Throughout Phase 2 and Phase 3 of clinical development, different capsule strengths and formulations have been used. A 150mg dosage strength (as hydrochloride salt) was developed for the Phase 3 formulation and for the proposed commercial formulation (presented as 123 mg free base). Table 3 summarizes all capsule formulations developed for use in clinical trials and provides comparison of these with the proposed commercial formulation. The pivotal Phase 3 and commercial formulations differ only in terms of (b) (4).

Table 3: Migalastat Hydrochloride Capsule Formulations Used in Clinical Trials and Proposed Commercial Formulations



B. BCS Designation

Reviewer's Assessment: the applicant classifies Migalastat Hydrochloride as BCS Class III

Solubility: Migalastat HCl has very high solubility across the physiological range and is freely soluble between pH 1.2 and pH 7.5 in aqueous media.

Table 4. Solubility of Migalastat Hydrochloride

Acid	
Phthalate Buffer	
Phosphate Buffer	
Phosphate Buffer	

Permeability: Migalastat HCl has low passive permeability, but well absorbed likely due to paracellular processes.

Dissolution: See below

C. Particle Size

In section 3.2.S.4.5 (Justification of Specification), the applicant stated that a specification for particle size distribution (PSD) is not proposed according to the guidance from ICH Q6A Decision Tree #3, based on the following justifications:

1) The particle size is not critical to solubility, dissolution, or bioavailability: the drug substance is very soluble across the physiological pH range. Aqueous solubility is greater than 500mg/mL. Predicting BCS Class III – absorption is not limited by dissolution.

2) The particle size is not critical to drug product content uniformity: the drug substance is screened (b) (4) to ensure that the particle size is appropriate to achieve good uniformity of content.

3) The particle size is not critical to drug product processability.

4) The particle size is not critical to drug product stability.

5) The particle size is not critical for maintaining product appearance: Migalastat HCl 150mg capsules are designed to be ingested intact without exposure of the capsule contents.

D. Dissolution Method and Acceptance Criteria

I. Proposed Dissolution Method and Acceptance Criteria

The following method parameters were used for in vitro dissolution testing

Table 5. Proposed Dissolution Method Parameters

(b) (4)

The proposed dissolution acceptance criteria for Migalastat Capsules 123mg is **Not Less Than** (b) (4) **% (Q) at 15 minutes.**

II. Dissolution Method Development

(b) (4)

V. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion for Migalastat Capsules 123mg is **Not Less Than (b)(4)% (Q) at 15 minutes**. Based on the dissolution profile, Migalastat reaches complete dissolution within 15 minutes. The dissolution acceptance criteria proposed by the Applicant is acceptable.

Reviewer's Assessment: ***Adequate***

The Applicant's justifications for choosing the proposed dissolution method parameters indicated as part of the method development is acceptable. The Applicant chose not to adopt dissolution test conditions and acceptance criteria with regards to discriminating power based on the ICH Q6A Decision Tree #7(2).

According to Dr. Hamid Shafiei's Drug Product Review, the analytical procedures for dissolution by HPLC has been appropriately established and validated (robust method).

The dissolution acceptance criteria proposed by the applicant is **Not less than (b)(4)% (Q) Migalastat released at 15 minutes**, which is acceptable.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: *N/A*

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: *N/A*

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: *N/A*

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: *N/A*

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: *N/A*

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: *N/A*

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: *N/A*

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: *N/A*

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: *N/A*

Bridging of Formulations

Reviewer's Assessment: *N/A*

Biowaiver Request

Reviewer's Assessment: ***N/A***

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

N/A

List of Deficiencies: **N/A**

Primary Biopharmaceutics Reviewer Name and Date:

Jae Wook Yoo, PharmD, 5/10/2018, 5/23/2018

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

Tien Mien (Albert) Chen, PhD, I concur. 05/20/18, 05/24/18

Acting Biopharmceutics Lead
DB/ONDP/OPQ

Appendix A

List of Information Requests (Chronological Order)

#1. IR (as cumulative comments) sent to applicant on 1/31/18

In 3.2.P.5.3 'Validation of Analytical Procedures', clinical batch W011194 mentioned in Table 8 and Table 11 is not listed as one of the batches in 3.2.P.5.4 'Batch Analyses' or in 2.7.1 'Biopharmaceutic Studies and Associated Analytical Methods'. Similarly, Batch W004735 mentioned in 3.2.P.2 'Pharmaceutical Development - Drug Product' (Table 4 and Figure 2) is not found as one of the batches used in the above sections as well. Verify whether the correct batch numbers were provided in all submissions and update all relevant sections as necessary.

Applicant's response to the IR (received on 2/16/2018):

Some bulk capsule batches have been packaged into multiple packaged batches with separate batch numbers. W011194 is a packaged batch that corresponds to bulk capsule batch W011176. Packaged batch W004735 corresponds to bulk capsule batch W004637. Data for both bulk capsule batches are provided in Module 3.2.P.5.4.

#2. IR (as cumulative comments) sent to applicant on 1/31/18

Submit the complete dissolution data including raw individual (n=12 capsules per batch), mean, SD, RSD, and mean profiles of the Migalastat Hydrochloride 150mg capsule batches used in the pivotal clinical studies. Also, provide the comparative dissolution data and profile with the batches of the proposed commercial formulations to demonstrate that the difference in (b) (4) (b) (4) *does not affect the dissolution performance. For dissolution studies, provide the specific batch number, manufacturing date, size, site, expiry date, and the date of dissolution test.*

Applicant's response to the IR (received on 2/16/2018):

Migalastat hydrochloride 150 mg capsule batches (W011176, W011177, W011178, W010397, W004637, W007078, and W010003) used in the pivotal clinical studies (AT1001-011 and AT1001-012) are presented in Table 2 of Module 2.7.1. Dissolution data (n=6, mean and % RSD) for these batches is

provided in Table 2 and Table 9 in Module 3.2.P.5.4 while batch details are provided in Table 1 and Table 8 in Module 3.2.P.5.4 respectively.

Comparative dissolution data (dissolution profile and individual results, n=12) to demonstrate that the difference (b) (4) *does not affect the dissolution performance are provided in Table 2 Module 2.3.P.2 Section 2.2.1.2 for two representative clinical batches of migalastat hydrochloride 150 mg capsule (W004637 and W011176).*

#3. IR sent to applicant on 02/25/18 (follow-up to IR #2)

It appears that we have not received adequate information that was requested in the previous communication. Previously we requested that you provide the complete dissolution profile data including raw individual (n=12 capsules per batch), mean, SD, RSD, and mean profile of Migalastat Hydrochloride 150mg capsule batches used in the pivotal clinical studies. The available dissolution data you were referring to in Module 3.2.P.5.4 only included mean (from 6 capsules only), range, and RSD. Please provide the complete dissolution information as requested above preferably in a complete table format (this applies to Batches W004637 and W011176 as well). We request that you provide the complete dissolution profile data from at least three registration/stability batches.

You have also referred to the comparative dissolution data of Batches W004637 and W011176 to demonstrate the effect of having (b) (4) (b) (4) *a Phase 3 Clinical (open-label) batch and a Primary Stability batch. Please also submit the comparative dissolution profile data with the proposed commercial (to-be-marketed) formulation (which you proposed to have different* (b) (4) *compared to the primary stability batch/registration batches) to see that the difference* (b) (4) *does not affect the dissolution performance.*

Finally, for all in vitro dissolution studies, include the specific batch number, manufacturing date, size, site, expiry date, and the date of dissolution test as part of the complete table mentioned above. Also, clearly label the specific packaged batch numbers to their specific corresponding bulk batches so that we can readily identify and locate all batches (bulk and packaged).

Applicant's responses to the IR (answers to different sections received separately on 3/12/18 and 4/6/18) are summarized in the review.

#4. IR sent to applicant on 3/28/18

Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the information specified below in the dissolution method development report (as a single document), if you have already submitted the specified information below, direct us to the appropriate section of the submission.

a. *Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the apparatus, in vitro dissolution media, rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). Clearly specify the testing conditions associated with each method development study. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45 60, etc. min).*

b. *Solubility data of the drug substance over the physiologic pH range.*

c. *Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, %CV at each time point and mean profiles]. Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim).*

Applicant's response to the IR (received on 4/10/18) is summarized in the review.

Jae Wook Yoo

Digitally signed by Jae Wook Yoo
Date: 5/24/2018 11:12:57AM
GUID: 56f16ff900504a151cca73200dd6150e

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 5/24/2018 11:10:14AM
GUID: 508da7240002a26723d38018ce005126

7 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

GALAFOLD™ (migalastat) capsules, for oral use
Initial U.S. Approval: YYYY

2) DOSAGE FORMS AND STRENGTHS

Capsules: 123 mg of migalastat. (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	GALAFOLD™ (migalastat)	Provided. **Satisfactory**
Dosage form, route of administration	capsules, for oral use	Provided. **Satisfactory**
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))	Capsules: 123 mg of migalastat	(b) (4) **Satisfactory**
Whether the drug product is scored	Not applicable	Not applicable

Revise "Dosage Forms and Strengths" from "Capsules: 123 mg of migalastat" to (b) (4)
(b) (4)

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

Capsules: 123 mg of migalastat in a size "2" (b) (4) capsule with an opaque blue cap and opaque white body with "A1001" printed in black, containing white to pale brown powder.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	size "2" (b) (4) capsule	Should be revised to: size "2" capsule **Unsatisfactory**
Strengths: in metric system	123 mg	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not provided.	Should be revised to include active moiety expression: 123mg migalastat provided as 150mg of migalastat hydrochloride **Unsatisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	size "2" (b) (4) capsule with an opaque blue cap and opaque white body with "A1001" printed in black, containing white to pale brown powder	Provided. But will be revised to include the statement of equivalence for the active moiety. See the suggested revision. **Satisfactory**

"Dosage Form and Strengths" section must be revised to include:

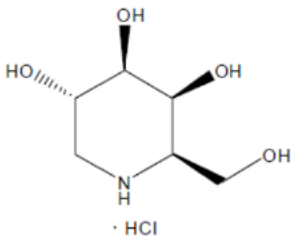
(b) (4)

The following revisions is recommended:

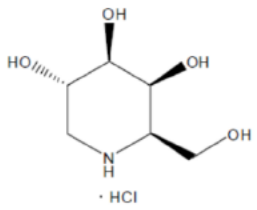
(b) (4)

2) #11: DESCRIPTION

(b) (4)



(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	GALAFOLD	Established name not provided. **Unsatisfactory**
Dosage form and route of administration	GALAFOLD is a pharmacological chaperone supplied in hard gelatin capsules each containing 123 mg of migalastat (equivalent to 150 mg migalastat hydrochloride) for oral administration	Provided but needs revision. **Unsatisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	123 mg of migalastat (equivalent to 150 mg migalastat hydrochloride)	Provided. **Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each GALAFOLD 123 mg capsule also contains magnesium stearate and pregelatanized (b) (4) starch. Ingredients in the shell capsule include gelatin, indigotine and titanium dioxide. Capsules are printed with ink consisting of black iron oxide, potassium hydroxide and shellac.	Provided. **Satisfactory**
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	GALAFOLD is a pharmacological chaperone	Provided but not adequate. **Unsatisfactory**
Chemical name, structural formula, molecular weight	Its chemical formula is $C_6H_{13}NO_4$•HCl. The molecular weight is 199.63 g/mol and the chemical structure is: 	The chemical name is not provided. **Unsatisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not provided	(b) (4) **Unsatisfactory**

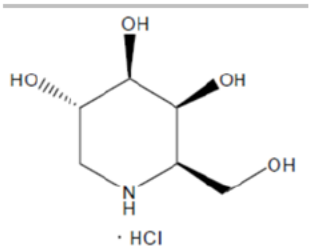
"Description" section must be revised to include:

1) Established name with the active moiety
2) The chemical name for the active ingredient
3) The proper pharmacological class.

The following revision is suggested:

(b) (4)

The chemical name migalastat hydrochloride is (+)-(2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl)piperidine-3,4,5-triol, hydrochloride. It has molecular formula of $C_6H_{13}NO_4$•HCl, molecular mass of 199.63g/mol and chemical structure:



Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble in aqueous media within the pH range of 1.2 to 7.5.

(b) (4)

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	GALAFOLD is supplied as (b) (4) (b) (4) 123 mg migalastat in size "2" (b) (4) capsules	Needs revision. Active moiety expression of strength with equivalence statement not provided. **Unsatisfactory**
Available units (e.g., bottles of 100 tablets)	Each pack size contains 14 capsules	Provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	size "2" (b) (4) capsules with an opaque blue cap and opaque white body with "A1001" printed in black	Provided but needs revision. **Unsatisfactory**
Special handling (e.g., protect from light)	Not applicable	Not applicable
Storage conditions	Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F)	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Amicus Therapeutics U.S., Inc. 1 Cedar Brook Drive Cranbury, NJ 08512 GALAFOLD™ is a trademark of Amicus Therapeutics, Inc.	Provided at the end of the PI. **Satisfactory**

"How Supplied/Storage and Handling" section must be revised to include:

(b) (4)

2) A concise description/identification of the dosage form.

The following revision is recommended:

Galafold (migalastat) Capsules, 123mg are size "2" capsule with opaque blue cap and opaque white body filled with white to pale brown powder and imprinted with "A1001" in black ink.

(b) (4)

Galafold capsules are packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks (28 days).

Wallet pack containing 14 Galafold capsules NDC XXXXX-YYYY-ZZ (the actual NDC number must be provided)

Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

II. Labels

(b) (4)

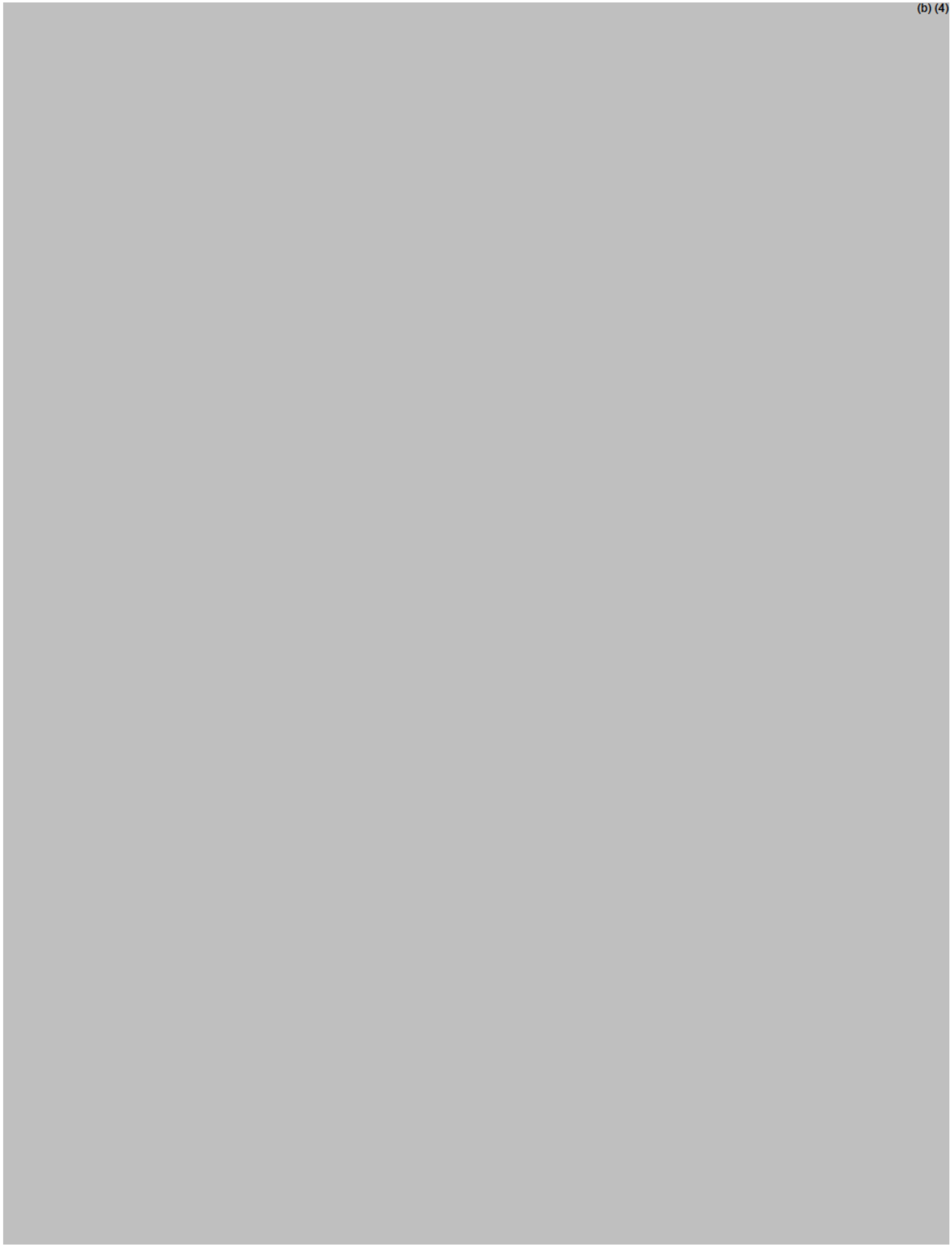
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Galafold™ (migalastat) capsules 123 mg	Provided. The size and prominence of the establish name look adequate. **Satisfactory**
Dosage strength	123 mg	Provided. **Satisfactory**
Net contents	Not displayed	Not provided. **Unsatisfactory**
"Rx only" displayed prominently on the main panel	Not displayed.	**Unsatisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Not displayed.	**Unsatisfactory**
Lot number and expiration date (21 CFR 201.17)	No displayed	Not provided. **Unsatisfactory**
Storage conditions	Not displayed.	Not provided. **Unsatisfactory**
Bar code (21CFR 201.25)	Not displayed.	Not provided. **Unsatisfactory**
Name of manufacturer/distributor	Displayed.	**Satisfactory**
And others, if space is available	GalafoldTM is to be taken every other day.	Provided. **Satisfactory.**

Revise the blister card inner sleeve labels to address the following:

1) display net content (14 capsules)
2) Display Rx only
3) Display NDC number.
4) Display lot number and expiration date
5) Display bar code
6) Display storage conditions

2. Blister Card Outer Sleeve (Carton)

(b) (4)



QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Gala migalast	Provided. The size and prominence of the establish name look adequate. The equivalence statement for the expression of active moiety is provided. **Satisfactory**
Dosage strength	123mg	Provided. **Satisfactory**
Net contents	14 capsules	Provided. **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	Displayed. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDC number location is displayed but actual the actual NDC number is not provided.	The actual NDC number is not provided. **Unsatisfactory**
Lot number and expiration date (21 CFR 201.17)	The location on the carton where the lot number and expiration will be placed has been designated.	Provided. **Satisfactory**
Storage conditions	(b) (4) . Store at USP Controlled Room Temperature 20-25°C (68-77°F)	Provided **Satisfactory**
Bar code (21CFR 201.25)	Displayed	Displayed. **Satisfactory**
Name of manufacturer/distributor	**MANUFACTURED BY:** (b) (4) **DISTRIBUTED BY:** Amicus Therapeutics U.S., Inc. Cranbury, NJ 08512	Displayed. **Satisfactory**

And others, if space is available	Each capsule contains 150 mg migalastat hydrochloride equivalent to 123 mg migalastat. Take on an empty stomach, at least 2 hours before or after food intake, at the same time each day. Swallow the capsule whole. Do not cut, crush, or chew the capsule. Read the package insert before use. Oral Use. Take Galafold capsule every other day and punch out the perforated circle on the blister sleeve on the days you are not taking Galafold. 	Provided **Satisfactory**

Add the actual NDC number to the blister card outer sleeve.

III. LIST OF DEFICIENCIES:

A. Regarding PI

Highlights:

Revise "Dosage Forms and Strengths" from "Capsules: 123 mg (b) (4) migalastat" to (b) (4)

Full Prescribing Information

#3: Dosage Forms and Strengths

Dosage Form and Strengths" section must be revised to include:

(b) (4)

The following revisions is recommended:

(b) (4)

#11: Description

"Description" section must be revised to include:

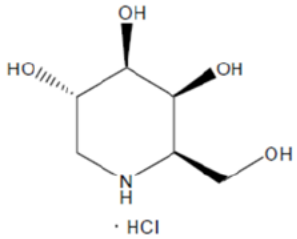
1) Established name for the active moiety

2) The chemical name for the active ingredient

3) The proper pharmacological class.

The following revision is suggested:

(b) (4)



Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble in aqueous media within the pH range of 1.2 to 7.5.

(b) (4)

#16: How Supplied/Storage and Handling

"How Supplied/Storage and Handling" section must be revised to include:

(b) (4)

4) A concise description/identification of the dosage form. The

The following revision is recommended:

(b) (4)

Galafold capsules are packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks (28 days).

Wallet pack containing 14 Galafold capsules NDC XXXXX-YYYY-ZZ (the actual NDC number must be provided)

Store at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

B. Regarding of the Container/Carton Labels:

a) Blister card inner sleeve label:

Revise the blister card inner sleeve labels to address the following:

1) Display net content (14 capsules)
2) Display Rx only
3) Display the actual NDC number.
4) Display lot number and expiration date
5) Display bar code
6) Display storage conditions

b) Blister card outer sleeve label:

Add the actual NDC number to the blister card outer sleeve

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies/revisions have been noted.
- Blister wallet (inner and outer sleeves) labels as provided do not display the required container closure information.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

Secondary Reviewer Name:

I agree with Dr. Shafiei's assessment on the labels and labeling, and concur with his conclusion that this application is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 5/01/2018 01:00:34PM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 6/11/2018 09:23:57AM
GUID: 502d0913000029f9798ca689a802fa55

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: April 25, 2018

To: Joseph Leginus, Drug Substance Reviewer
Hamid Shafiei, Drug Product Reviewer
Hitesh Shroff, Acting CMC Lead
Oumou Barry, Methods Verification Project Manager

Through: Jason Rodriguez, Ph.D., Acting Director, CDER/OPQ/OTR/DPA

From: Tim Andres Marzan, Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, Ph.D., Project Manager, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 208623: Galafold (Migalastat) Capsule, (b) (4) mg

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Drug Substance – Identification by IR Spectroscopy
2. Drug Substance – Identity and Assay of M014428FP by HPLC-CAD (Analytical Method AVM014428FP, Version 07)
3. Drug Product – Identification and Assay of Migalastat 123 mg Capsules by HPLC-CAD (Quality Control Method QCM1200/02).
4. Drug Product – Dissolution of Migalastat 123 mg Capsules using HPLC-CAD Detection (Quality Control Method QCM1199/02).

The following methods could not be fully evaluated in the laboratory due to instrument limitations:

1. Drug Substance – Drug Related Impurities by HPLC-CAD (Analytical Method AVM014428FP, Version 07)
2. Drug Substance – Drug Related Impurities by HILIC-CAD (Analytical Method AVM014428FP, Version 07)
3. Drug Product – Drug Related Impurities by HPLC-CAD (Quality Control Method QCM1200/02).

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods, based on review of the methods:

1. Although DPA was not able to adequately evaluate the methods used for the drug substance and drug product related impurities by HPLC-CAD (Analytical Method AVM014428FP, version 07 and Quality Control Method QCM1200/02 respectively) due to sensitivity limitations of DPA's Charged Aerosol Detector (CAD), it should be noted that the (b) (4) impurity peak has a relative retention time (RRT) of (b) (4) and a capacity factor (k') of about (b) (4). Ideally, peak capacity factors should be around (b) (4) or greater to avoid interferences from peaks eluting at the void volume. DPA recommends the optimization of the capacity factor for (b) (4) impurity peak.

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f881a975cd

Summary of Analysis

1. Drug Substance

1.1. Identification by IR Spectroscopy - Pass

The spectrum of the sample is concordant with that of Migalastat Hydrochloride reference material.

1.2. Migalastat Content by HPLC (% w/w, "as is") - Pass

Sample	% w/w	Specification
Sample Preparation 1 - 1	(b) (4)	
Sample Preparation 1 - 2		
Sample Preparation 2 - 1		
Sample Preparation 2 - 2		
Average		(b) (4)

2. Drug Product

2.1. Identification of Migalastat Hydrochloride by HPLC – Pass

Sample	Retention Time (min)
Migalastat HCl Standard (n = 6)	(b) (4)
Sample Preparation 1 (n = 3)	
Sample Preparation 2 (n = 3)	

2.2. Migalastat Content by HPLC (% Label Claim) – Pass

Sample	% Label Claim	Specification
Sample Preparation 1 - 1	(b) (4)	
Sample Preparation 1 - 2		
Sample Preparation 1 - 3		
Sample Preparation 2 - 1		
Sample Preparation 2 - 2		
Sample Preparation 2 - 3		
Average		(b) (4)

2.3. Dissolution (% Migalastat released) – Pass

Capsule	% Released	Specification
1	(b) (4)	
2		
3		
4		
5		
6		
Average		**Not less than (b) (4) % (Q) at 15 minutes**

Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 208623 Migalastat Capsules, 123 mg

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Assay of the the drug substance, (b) (4) is determined by the in-house validated HPLC method. During manufacturing process development critical steps were identified and in process controls (IPC) (b) (4) were instituted for a robust manufacturing process and to constistantly produce quality DP. The content uniformity was assessed per USP <905> by (b) (4) method. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters • Container/closure system	L	The related substances/ impurities are fully characterized and controlled by DS specification. The impurities are also controlled by (b) (4) The impurities are assessed by (b) (4) method.	Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The particle size of the drug substance is controlled (b) (4) (b) (4) during the drug product manufacturing process. Dissolution is controlled by DP specification.	Low to None	None