CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208854Orig1s000

CHEMISTRY REVIEW(S)

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NDA-208854-ORIG-1 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle

Inspection Management Form

Inspection Management Form

As of Mar 23, 2017 7:54 am GMT

Inspection Management Form

NDA-208854-ORIG-1

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility

SHIONOGI PHARMA CHEMICALS CORPORATION LTD | 3008353674 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

Overall Manufacturing Inspection Recommendation

- (●) Approve
- ( ) Withhold
- ( ) No Evaluation Necessary

Save Cancel

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name
Approve Facility	3/21/2017	NDA-208854-ORIG-1	3008353674	694137266	110006261	SHIONOGI PHARMA CHEMICALS CORPORATION
Approve Facility	6/14/2016	NDA-208854-ORIG-1				(b) (4)
Approve Facility	4/15/2016	NDA-208854-ORIG-1				

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Assigned To

Donald Lech

Edit Assignment

This was done on
Mar 21, 2017
(2 days ago)

Status
Complete

This task is waiting on
Facilities

Last Update
Mar 21, 2017

Submitted On
Mar 24, 2016

Reference Number
7189402

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

Date: **March 9, 2017**

From: **Hitesh Shroff, Ph.D.**
CMC Lead (Acting)
Branch V/Division of New Drug Products II
ONDP/OPQ

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

To: **CMC Review #1 of NDA 208854**

Subject: **Final Recommendation**

The CMC review #1 was based on proposed draft labeling/label and, although it was deemed acceptable as they were, but final approval recommendation was pending.

On February 23, 2017, the revised label and labeling were submitted with some editorial changes from the original draft labeling and those changes as noted below are deemed acceptable from the OPQ perspective.

1. In Highlight section of PI,

   SYMPROIC® (naldemedine) tablets, for oral use
   Initial U.S. Approval: 2017

   Was changed to

   SYMPROIC® (naldemedine) tablets, for oral use, C-X
   Initial U.S. Approval: 2017

2. In **#3 Dosage and Strength** section of PI

   Equivalency statement is deleted.

   *This is acceptable since the equivalency statement is in the Description section.

3. In **#11 Description** section of PI,

   SYMPROIC (naldemedine), an opioid (b) (4) *antagonist, contains naldemedine tosylate as the active ingredient.*

Was changed to,

SYMPROIC (naldemedine), an opioid antagonist, contains naldemedine tosylate as the active ingredient.

**Deletion of* (b) (4) *is acceptable.*

4. In **How Supplied/ Storage and Handling** section of PI

SYPROIC 0.2mg tablets are supplied in a bottle of 90 tablets-NDC 59630-222-90

Was changed to,

SYMPROIC is supplied as 0.2 mg naldemedine tablets in a bottle of 90 tablets - NDC 59630-222-90.

*This editorial change is acceptable

Recommendation:

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

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 3/09/2017 01:54:56PM
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Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 3/09/2017 01:42:49PM
GUID: 502d1ab500002afd219fd67e3b9c99c8

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 208854
Review 1

Drug Name/Dosage Form	Symproic (naldemedine) tablets
Strength	0.2 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Shionogi Inc., Florham Park, NJ
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	3/23/2016	OPQ
Amendment	4/19/2016	ONDP
Amendment	5/19/2016	ONDP
Labeling Amendment	7/05/2016	ONDP
Labeling Amendment	7/15/2016	ONDP
Amendment	8/10/2016	ONDP/DB
Amendment	8/19/2016	ONDP/OPF
Amendment	8/22/2016	ONDP
Amendment	8/29/2016	ONDP
Amendment	9/19/2016	ONDP/OPF
Amendment	9/30/2016	ONDP/OPF
Labeling Amendment	9/30/2016	ONDP
Labeling Amendment	10/07/2016	ONDP

QUALITY ASSESSMENT

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Sarah Ibrahim	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Zhao Wang	CDER/OPQ/OPF/ DPAI/PABI
Microbiology	Zhao Wang	CDER/OPQ/OPF/ DPAI/PABI
Facility	Donald Lech	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Peng Duan	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Cheronda Cherry-France	CDER/OND/ODEIII/ DGIEP
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
Environmental Analysis (EA)	James Laurenson	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	Adequate	05/06/2016 by Ping Jiang-Baucom, PhD	DATE OF LAST UPDATE OF DMF: 04/29/2016
	III			Adequate	09/07/2010 By BANERJEE, ANAMITRO	DATE OF LAST UPDATE OF DMF: 04/16/2016 includes list of authorizations and annual report with no changes to DMF.
	III			N/A	N/A	N/A
	III			Adequate	02/08/2016 by THEOPHIN, CLAUDE	DATE OF LAST UPDATE OF DMF: 01/20/2016
	III			Adequate	02/14/2012 by Gene W. Holbert, Ph.D.	DATE OF LAST UPDATE OF DMF 09/30/2014 list companies for which LOA's provided and DMF remains Adequate for packaging of solid (b) (4) dosage forms.

(b) (4)		(b) (4)			
	III		Adequate	September 26, 2014 by JIANG-BAUCOM, PING	Date of Last Update of DMF: June 27, 2014, Information related to the (b) (4)
	III		N/A	N/A	N/A
	III		Adequate		As of 08/19/2014 the only submission to the DMF is Administrative Change/Holder; Administrative Change/ Contact at Holder

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107475	Naldemedine tablets for treatment of opiod-induced constipation also from Shionogi Inc..

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 as of this review.

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

The label/labeling issues have ***not*** been completely resolved as of this review.

Therefore, from the OPQ perspective,this NDA is ***not*** deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) until the above issues are satisfactorily resolved. (**see Attachment II**)

II. Summary of Quality Assessments

A. Product Overview

Symproic (naldemedine) tablets, 0.2 mg are immediate release, yellow, round film-coated tablets debossed with Shionogi marking and 222 on one side and 0.2 on the other side. Each tablet contains 0.2 mg naldemedine (equivalent to 0.26 mg Naldemedine Tosylate). Symproic tablets are supplied in high-density polyethylene (HDPE) bottle and closed (b) (4) with an aluminum foil induction seal liner. A silica gel desiccant is included in the bottle. Each bottle contains 90 tablets. The tablets may also be supplied (b) (4)

Proposed Indication(s) including Intended Patient Population	Symproic (naldemedine) tablets are indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
Duration of Treatment	(b) (4)
Maximum Daily Dose	0.2 mg per day
Alternative Methods of Administration	**N/A**

Quality Assessment Overview

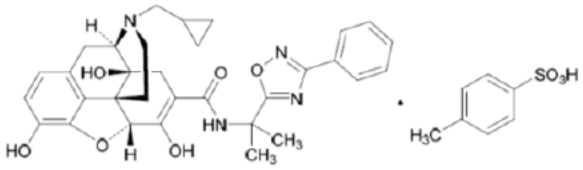
Drug Substance:

The drug substance, naldemedine tosylate, is a peripherally-acting μ-opioid receptor antagonist (PAMORA). It is manufactured, tested and released by Shionogi Pharma Chemicals Co. Ltd., Tokushima, Japan.

Naldemedine tosylate is a white to light tan powder. It has four chiral centers. The preferred (b) (4) is generated by the manufacturing process. It is non-hygroscopic. It is slightly soluble in water but even less soluble in common organic solvents. It belongs to BCS Class III (low permeability, high solubility) drug substances.

(b) (4)

The chemical name of naldemedine tosylate is 17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14-trihydroxy-*N*-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan -7-carboxamide 4-methylbenzenesulfonic acid. Its molecular formula is $C_{32}H_{34}N_4O_6 \cdot C_7H_8O_3S$ and molecular weight is 742.84. The molecular weight of naldemedine (free base) is 570.25. The structural formula of the drug substance, naldemedine tosylate, is the following:



naldemedine Tosylate

The quality of the drug substance is controlled by a specification that includes identification by IR and UV; assay and impurities by HPLC and particle size by (b) (4) The specification is deemed adequate per Drug Substance reviewer, Dr. Joseph Leginus (see his drug substance review).

The bulk drug substance is packaged (b) (4)

Based on the acceptable stability data, the proposed restet period of (b) (4)-month is

justified when stored in the proposed container closure system (b) (4)

Drug Product:
Symproic (naldemedine) tablets, 0.2 mg contains naldemedine tosylate as the active pharmaceutical ingredient and the following inactive ingredients: D-mannitol, croscarmellose sodium and magnesium stearate. (b) (4) hypromellose, talc and yellow ferric oxide.

(b) (4)

The drug product quality is controlled by a specification that includes identification by visual, UV and HPLC; assay and related substances (specified, unspecificed and total) by HPLC, content uniformity, disintegration and dissolution etc. The specification is deemed adequate per Drug Product reviewer, Dr. Sarah Ibrahim (see the drug product review).

The Division of Pharmaceutical Analysis, FDA, verified four drug substance and five drug product analytical procedures. The method validation report dated 22 Sep, 2016 stated that these methods were verified and found acceptable for quality control and regulatory purposes **(see Attachment I).**

On the basis of the satisfactory stability data of drug product packaged in bottles (b) (4) 36-month of expiration dating period from the date of the manufacture of the drug product including holding time is justified when stored at room temperature in the proposed (b) (4) bottles.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included.The claim was reviewed by Dr. James Laurenson and found to be acceptable (see his environmental analysis review).

The identity, strength, purity and quality of the drug product are assured by the adequate raw material controls, validated manufacturing process and drug product specification.

B. Special Product Quality Labeling Recommendations (NDA only)
None

Final Risk Assessment (see Attachment III)

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ENVIRONMENTAL ANALYSIS

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA has assessed the claim and found it to be acceptable.

R Regional Information

Environmental Analysis

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) for naldemedine tablets 0.2 mg, with naldemedine tosylater as the active ingredient. The claim is based on 21 CFR 25.31(b), which is for substances that will increase in use but for which the estimated introduction concentration (EIC) at the point of entry into the aquatic environment is below 1 ppb. A calculation for an EIC of (b) (4) ppb, based on an estimated use of (b) (4) kg/year of active ingredient, supported this claim. A statement of no extraordinary circumstances per 21 CFR 25.21 also was provided.

Reviewer's Assessment:

The EIC calculation appears appropriate for the estimated amount of drug to be produced for direct use. The EIC is (b) (4) times lower than the 1 ppb categorical exclusion concentration. Furthermore, based on a brief review of the clinical and nonclinical toxicity data and mechanism of action for this substance, no hormonal signals appear to exist. The required statement of no extraordinary circumstances also exists. Therefore, this claim for a categorical exclusion from an EA is acceptable.

Primary EA Reviewer Name and Date: Jim Laurenson, 11/17/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 11/17/2016

Michael Furness

Digitally signed by Michael Furness
Date: 11/21/2016 08:38:18AM
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James Laurenson

Digitally signed by James Laurenson
Date: 11/17/2016 08:32:18PM
GUID: 51dc6bdb0000c62de59b85452e59746f

APPEARS THIS WAY ON ORIGINAL

LABELING

R Regional Information

As of 10/07/2016

1.14 Labeling

Labeling & Package Insert

A. Package Insert

(a) "Highlights" Section (21CFR 201.57(a)

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

SYMPROIC (naldemedine) tablets for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

SYMPROIC is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. (1)

----------DOSAGE AND ADMINISTRATION----------

- (b) (4)
- Alteration of analgesic dosing regimen prior to initiating SYMPROIC is not required (2.1)
- (b) (4)
- Discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued (2.1)

(b) (4) dosage:
0.2 mg once daily with or without food (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet: 0.2 mg naldemedine (3)

----------CONTRAINDICATIONS----------

- Patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction (4, 5.1)
- (b) (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor symptoms of opioid withdrawal (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reactions (b) (4) are diarrhea, abdominal pain, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at (b) (4) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A inhibitors (e.g., itraconazole): Increased naldemedine concentrations, (b) (4) monitor for adverse reactions (b) (4)
- Strong CYP3A inducers (e.g., rifampin): Decreased naldemedine concentrations: (b) (4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May precipitate opioid withdrawal in a fetus (8.1)
- Lactation: Discontinue drug or (b) (4) taking into consideration importance of drug to mother (8.2)
- Hepatic Impairment: Avoid in severe impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2016

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: SYMPROIC (naldemedine) tablets for oral use	Proprietary name is presented correctly. The established name is presented correctly. **Satisfactory.**
Dosage form, route of administration	Dosage: Tablet: 0.2 mg naldemedine	The dosage form "tablet" is described adequately. **Satisfactory.**
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablet: 0.2 mg naldemedine	The strength of the tablet is expressed similar to previously approved dosage forms. **Satisfactory.**

Conclusion:

1- **Proprietary name Symproic has been accepted and package insert includes the correct proprietary name and the proposed labeling.**
2- **The dosage form is clearly described and adequately summarized.**
3- **The strength of the dosage form is Adequate .**

This section is **Satisfactory.**

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

Tablets: 0.2 mg naldemedine (equivalent to 0.26 mg of naldemedine tosylate); supplied as yellow, round, film-coated, debossed with Shionogi marking above the identifier code 222 on one side and 0.2 on the other side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Dosage form is presented correctly. **Satisfactory.**
Strengths: in metric system	0.2 mg naldemedine (equivalent to 0.26 mg of naldemedine tosylate)	The strength of the tablet is expressed in the base form and is Adequate. **Satisfactory.**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	supplied as yellow, round, film-coated, debossed with Shionogi markingabove the identifier code 222 on one side and 0.2 on the other side.	The description of the tablet is concise and accurate. **Satisfactory.**

Conclusion:

1. The description of the identifying characteristics of the tablet is adequately expressed.
2. The strength is expressed as the base form of the drug.

This section is **Satisfactory.**

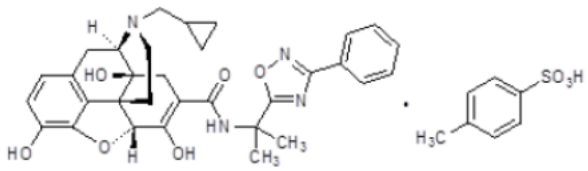
#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

SYMPROIC (naldemedine) (b) (4), an opioid (b) (4) antagonist, contains naldemedine tosylate as the active ingredient.

The chemical name for naldemedine tosylate is: 17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide 4-methylbenzenesulfonic acid.

The structural formula is:



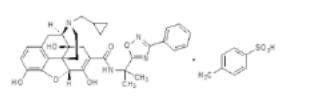
The empirical formula for naldemedine tosylate is $C_{32}H_{34}N_4O_6 \cdot C_7H_8O_3S$ and the molecular weight is 742.84.

Naldemedine tosylate is a white to light tan powder, soluble in dimethylsulfoxide and methanol, slightly soluble in alcohol and water; is independent of pH.

SYMPROIC (naldemedine) tablets for oral use contain 0.2 mg of naldemedine equivalent to 0.26 mg of naldemedine tosylate.

Excipients are: D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	SYMPROIC (naldemedine) tablets,	Proprietary name is correct. The established name is presented correctly and contain dosage form, tablets. **Satisfactory.**
Dosage form and route of administration	SYMPROIC (naldemedine) tablets for oral use	The dosage form and route are expressed correctly. **Satisfactory.**
Active moiety expression of strength with equivalence statement for salt (if applicable)	contain 0.2 mg of naldemedine equivalent to 0.26 mg of naldemedine tosylate.	The equivalency statement is properly placed per MAPP 5021.1. **Satisfactory.**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Excipients are: D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide.	The inactive ingredients information is presented correctly. **Satisfactory.**
Statement of being sterile (if applicable)	Absent	Not applicable. **Satisfactory**
Pharmacological/ therapeutic class	an opioid (b) (4) antagonist	This will be determined in the labeling meeting.

		Satisfactory
Chemical name, structural formula, molecular weight	3,6,14-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide 4-methylbenzenesulfonic acid. The structural formula is:  The empirical formula for naldemedine tosylate is $C_{32}H_{34}N_4O_6 \cdot C_7H_8O_3S$ and the molecular weight is 742.84.	The chemical names and the structural formula are correct. The molecular weight is included. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	NA

Conclusion:

1. Established name is consistently expressed as "SYMPROIC (naldemedine) tablets"
2. The equivalency statement is properly placed, per MAPP 5021.1, and included as follows: "….contain 0.2 mg of naldemedine (equivalent to 0.26 mg naldemedine tosylate)".
3. The chemical structures and formula are expressed correctly.
4. The strength of the dosage form is expressed correctly and in accordance to USP salt policy,
5. The molecular weight of the drug substance is included.

This section is **Satisfactory.**

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMPROIC (b) (4) are supplied in a bottle of 90 tablets - NDC 59630-222-90.

Store SYMPROIC in light resistant container at 20-25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	0.2 mg tablets	The information provided is Adequate. **Satisfactory.**
Available units (e.g., bottles of 100 tablets)	supplied in a bottle of 90 tablets	The information provided is Adequate. **Satisfactory.**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 59630-222-90	The information provided is Adequate. **Satisfactory.**
Special handling (e.g., protect from light, do not freeze)	Store SYMPROIC in light resistant container	Statement is present. **Satisfactory.**
Storage conditions	Store SYMPROIC in light resistant container at 20-25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].	The information provided is Adequate. **Satisfactory.**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	SYMPROIC is a trademark of the Shionogi group. Manufactured for: Shionogi Inc., 300 Campus Drive, Florham Park, NJ 0793	**Satisfactory.**

Conclusion:

1. The strength of the dosage form is expressed accurately under section 16.
2. Section 16 includes Available units, NDC number, Special handling and Storage conditions.
3. The package insert section 17 includes the manufacturer/distributor name.

This section is **Satisfactory.**

B. Immediate Container Label and Carton

QUALITY ASSESSMENT

(b) (4)

Reviewer's Assessment:

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Symproic (Naldemedine) tablets 0.2 mg	The dosage form and strength are included. **Satisfactory.**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Each tablet contains: 0.2 mg of naldemedine (equivalent to 0.26 mg of naldemedine tosylate)	**Satisfactory.**
Net contents (21 CFR 201.51(a))	Displayed	**Satisfactory.**
Lot number per 21 CFR 201.18	Displayed	**Satisfactory.**
Expiration date per 21 CFR 201.17	Displayed	**Satisfactory.**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not Displayed	**Satisfactory.**
Sterility Information (if applicable)	Not Applicable	**Satisfactory.**
"Rx only" statement per 21 CFR 201.100(b)(1)	Displayed	**Satisfactory.**
Storage Conditions	Displayed	**Satisfactory.**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	**Satisfactory.**
Bar Code per 21 CFR 201.25(c)(2)**	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
"See package insert for dosage information" (21 CFR 201.55)	Displayed	**Satisfactory.**
"Keep out of reach of children" (optional for Rx, required for OTC)	Not Displayed	**Satisfactory.**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Displayed	**Satisfactory.**

1. ***The Proprietary name, established name and strength are adequately expressed.***

2. Net content, lot number, expiration date, manufacturer, and storage conditions are clearly displayed.

3. NDC number and Bar code are adequately displayed.

This section is Satisfactory.

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date:

The labeling/label issues have been satisfactorily resolved, and therefore, the application is recommended for approval from the labeling and label perspective.

Sarah Ibrahim, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Drug Product Reviewer Name and Date:

I agree with Dr. Ibrahim's assessment of the labeling and labels and her recommendation that the application be approved from the labeling/label perspective.

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

Moo Jhong Rhee

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FACILITIES

Product Background: This drug product is indicated for the treatment of opioid-induced constipation (OIC) in subjects with chronic non-cancer pain opioid therapy.

NDA/ANDA: NDA-208854-ORIG-1

Drug Product Name / Strength: Symproic (Naldemedine Tosylate) Tablets || 0.2 mg

Route of Administration: Oral

Applicant Name: Shionogi Inc.

Review Summary: The overall assessment for NDA 208854, Symproic (Naldemedine Tosylate) Tablets is Approve. This decision is based on the current acceptable final recommendations for each of the three firms listed.

List Submissions being reviewed (table): N/A

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: No apparent outstanding issues.

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Shionogi Pharma Chemicals Co., Limited Japan	3008353674	API manufacturing, packaging, and release and stability testing – CSN	• Moderate	• Acceptable

Reviewer's Assessment:

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(b) (4)

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

None at this time.

List of Deficiencies: None

Primary Facilities Reviewer Name and Date: Donald Lech October 19, 2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Juandria Williams, PhD; DIA/B3 October 21, 2016

Donald Lech

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Date: 10/21/2016 03:57:16PM
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Juandria Williams

Digitally signed by Juandria Williams
Date: 10/21/2016 04:00 28PM
GUID: 513b65ab0005b7cb48614cd3d341d717

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208854

Drug Product Name / Strength: Naldemedine 0.2 mg immediate release tablets

Route of Administration: Oral

Applicant Name: Shionogi

Review Summary:

Naldemedine is a peripherally-acting μ-opioid receptor antagonist (PAMORA) being developed by Shionogi as a once daily treatment for opioid induced constipation (OIC). The recommended dose and dosing regimen for naldemedine is a single 0.2 mg tablet, once daily, without regard to food. Table 1 shows the composition of the proposed drug product.

Table 1. Composition of the proposed 0.2 mg Naldemedine Tablets.

Component	Amount per Tablet (mg/tablet)	Function	Quality Standard
Naldemedine Tosylate[a]	0.26 (b) (4)	Active Ingredient	In-house standard
D-Mannitol	(b) (4)		USP/Ph.Eur./JP
Croscarmellose Sodium			NF/Ph.Eur./JP
Magnesium Stearate			NF/Ph.Eur./JP
			(b) (4)

a Equivalent to 0.2 mg of naldemedine.

(b) (4)

BCS Designation

Reviewer's Assessment:

Solubility:

The solubility of naldemedine under different pHs is shown in Table 2.

Table 2. Solubility of naldemedine tosylate

Test solution temperature: 37°C
Sampling Time: 2 hours after the reconstitution

Media	pH (Actual)	Solubility (µg/mL)
JP dissolution fluid 1	1.2	1736
SGF	1.2	2066
pH 2 [a)]	2.0	1795
pH 4 [a)]	4.0	1791
FeSSIF	5.0	1179
pH 6 [a)]	6.0	983
Water	6.1	1373
FaSSIF	6.5	533
JP dissolution fluid 2 [b)]	6.9	772
pH 7.5 [a)]	7.5	735
pH 10 [a)]	10.0	2326
pH 12 [a)]	12.0	8603

a) Britton-Robinson buffer
b) Phosphate buffer
FaSSIF: fasted state simulated intestinal fluid
FeSSIF: fed state simulated intestinal fluid
SGF: simulated gastric fluid

As Table 2 shows, naldemedine has a high solubility over pH 1-pH 12 (soluble of 200µg with 250 mL of fewer medium).

Permeability:

In vitro permeability study using Caco-2 cell found that the apical to basal (A-B) Papp values for naldemedine were 1.99 ± 0.815 x 10^{-6} cm/sec and 1.63 ± 0.142 x 10^{-6} cm/sec with the dosing strength of 140 nM and 1400 nM (10% and 100% of the proposed highest dose strength in 250 mL) in unidirectional study. The permeability of naldemedine was lower than that of minoxidil, a marker for the high permeability class compound. Therefore, naldemedine could be classified as low permeability compound based on the study in Caco-2 cells.

Dissolution:

See followings.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

The proposed dissolution is shown in Table 3.

Table 3. Dissolution parameters

Parameters	Specified Value
Dissolution Apparatus	USP Apparatus II/Ph.Eur. and JP Apparatus 2 (Paddles)
Dissolution Media	A mixture of pH 6.8 phosphate buffer solution and water (1:1)
Volume of Dissolution Media	500 mL
Temperature	37 ± 0.5°C
Paddle Speed	50 rpm
Sampling	(b) (4) minutes
(b) (4)	(b) (4)

1. Selection of dissolution medium

(b) (4)

(b) (4) the selection of 1:1 mixture of water and JP dissolution fluid 2 is acceptable.

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(b) (4)

4. Dissolution acceptance criterion

The proposed dissolution acceptance criterion is NLT (b) (4)% in (b) (4) min.

Figure 3 shows the dissolution profiles of three primary registration batches (Batch 1211081 is clinical batch). Table 5 shows the dissolution data of the three batches.

Figure 3. Dissolution profiles of three primary registration batches (#1211081 clinical batch)

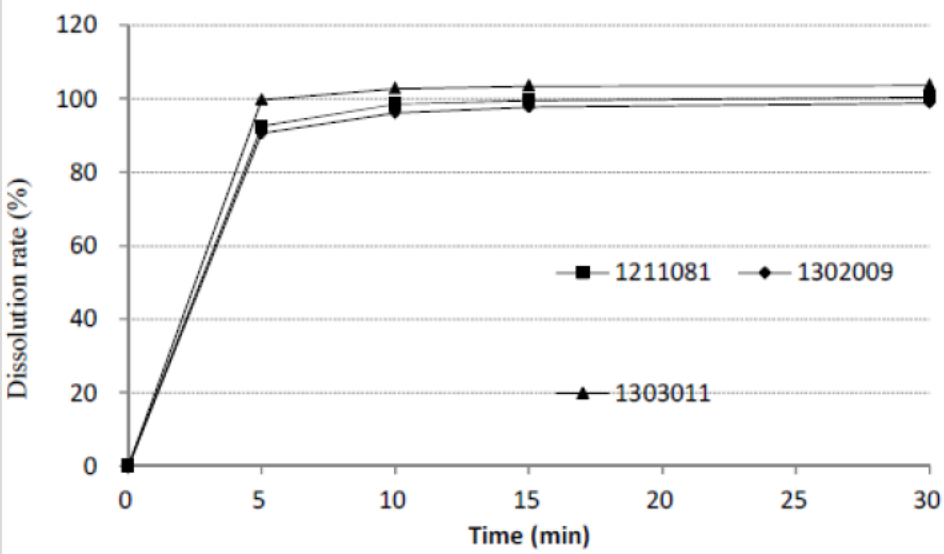


Table 5. Results of Dissolution Test (%)

Batch Number		Dissolution Rate (%)		
		1211081	1302009	1303011
Time (Min)	5	(b) (4)		
	Mean	92.6	90.7	99.8
	10	(b) (4)		
	Mean	98.6	96.2	102.9
	15	(b) (4)		
	Mean	99.7	97.7	103.6
	30	(b) (4)		
	Mean	100.6	98.9	103.8

As Table 5 and Figure 4 show, the drug release in three batches is very rapid, and reaches more than (b) (4)% of release (b) (4) min. Table 6 shows the drug release of three batches tested at (b) (4) min by triplicate analysis, and all of the units released more than (b) (4)% in (b) (4) min. Therefore,

based on Figure 3 and 4, Table 5, and Table 6, the proposed dissolution acceptance criterion can be (b) (4) % in 10 min.

Table 6. Single point dissolution obtained by triplicate analyses for the three batches

Batch Number	1211081			1302009			1303011		
Repetition	1	2	3	1	2	3	1	2	3
No. 1	(b) (4)								
No. 2									
No. 3									
No. 4									
No. 5									
No. 6									
Mean	101.4	100.7	100.7	98.8	99.5	98.9	101.4	101.7	101.5
Min.	100.2	99.9	98.5	96.7	97.3	97.1	100.3	100.8	100.7
Max	103.4	101.8	101.9	100.5	101.4	100.0	102.8	102.3	102.6

Figure 4. Dissolution profiles of three batches (1211081, 1302009, and 1303011) (Dotline: represents the proposed Q value (b) (4) %).

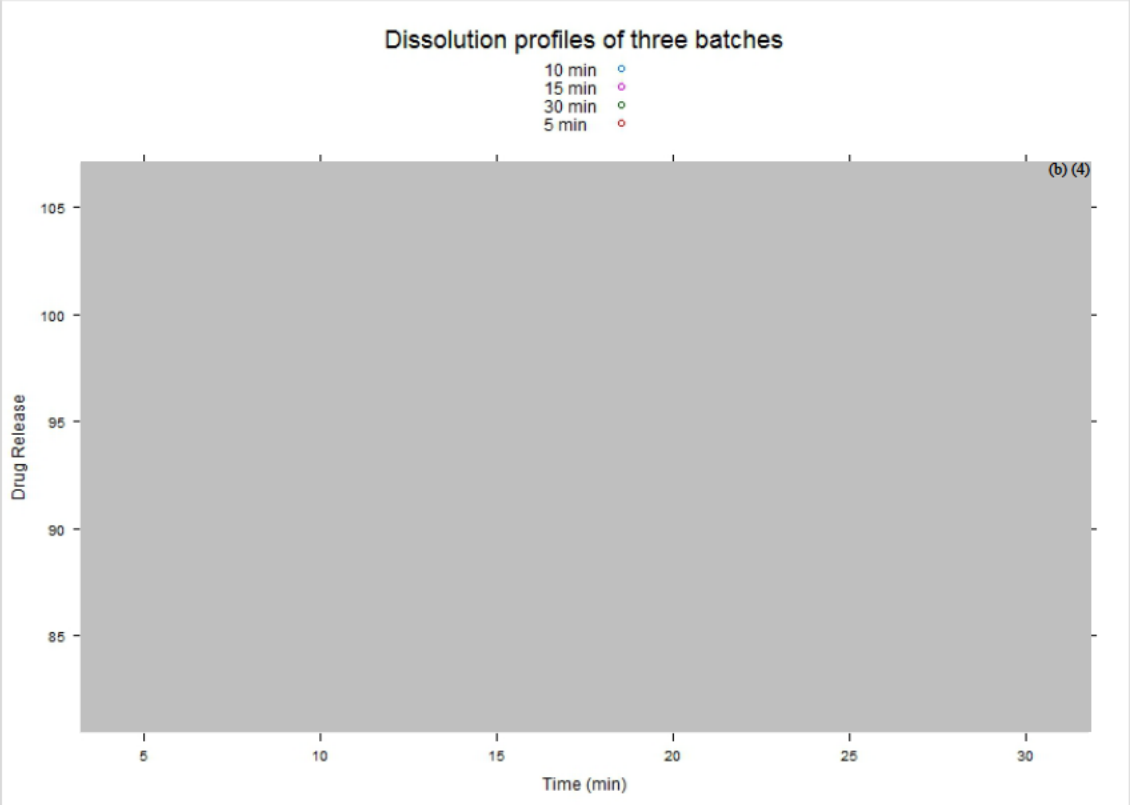
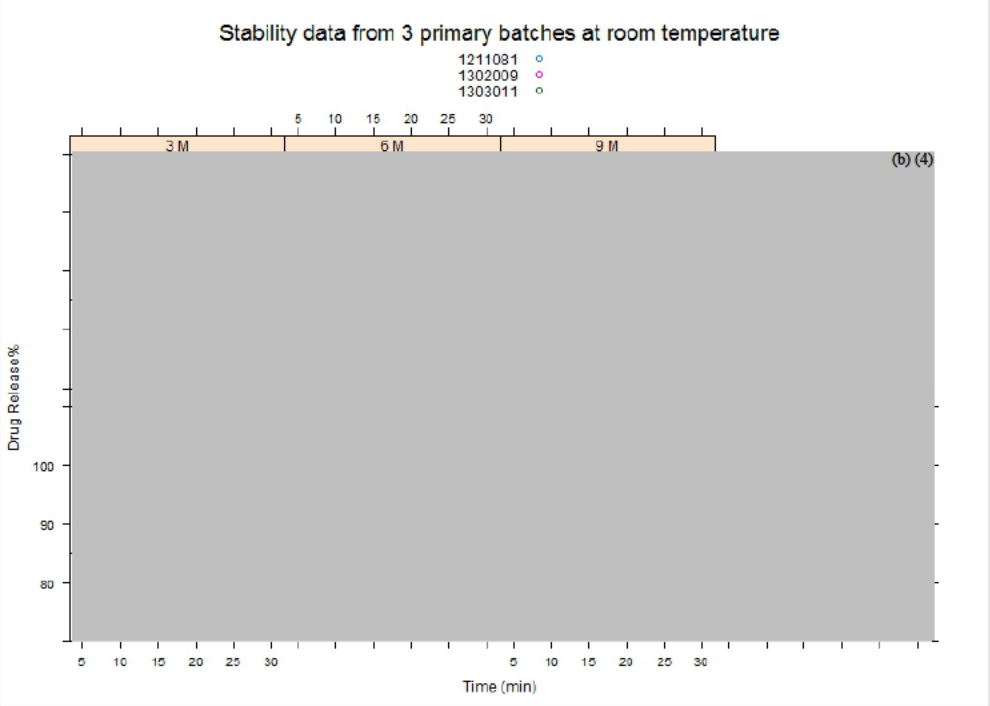


Figure 5 shows the release test conducted for three primary stability batches storage at 25°C/60% RH up to 24 months. Dotline represents the Q of (b) (4)%. However, the Applicant only provided the mean data of the six tested tablets, without CV%. Although all the mean values at each sampling time points passed the (b) (4)%, we recommend the Applicant provide individual release data for each tested tablets.

Figure 5. Dissolution data from 3 primary stability batches tested at 25°C/60% RH



Furthermore, since dissolution has limited discriminatory ability to detect the variations in formulation or manufacturing attributes, the ability of the current proposed dissolution method to reject unqualified batch might be restricted. Therefore, incorporating the disintegration test as an alternative way for quality control might be necessary.

Information requests as follows were conveyed to the Applicant on July 26, 2016:

FDA Request:

1. Submit complete dissolution data (include individual, mean +/- SD, mean dissolution profile) for stability data of three primary stability batches (1211081, 1302009, and 1303011) tested at 25°C/60% RH.

2. We recommend (b) (4) the proposed dissolution acceptance criterion to NLT (b) (4)% in 10 min.

We request that you acknowledge your acceptance of the recommended dissolution acceptance criterion. Implement the recommended dissolution acceptance criterion for future SUPAC manufacturing changes of your proposed drug product, and provide the revised specifications table in M3.5.1 with the updated acceptance criterion for the dissolution and stability test.

3. In the meantime, your proposed drug product releases very rapidly using the proposed dissolution method (e.g. more than (b) (4) % of labelled amount of drug) is released within 10 min). There is limited discriminatory ability for your proposed dissolution method. Although the current dissolution method is needed, we recommend you to develop disintegration test (as described in guidance ICHQ6A: Decision tree (b) (4)) for quality control purpose (release and stability testing). Alternatively, you can consider applying modeling approaches such as physiologically based pharmacokinetic (PBPK) modeling to show that the proposed dissolution method can reject drug product batches with unsatisfied in vivo performance.

The Applicant provided the complete dissolution data we required on IR 1, and acknowledged their acceptance of our recommended dissolution acceptance criterion of Q= (b) (4) % in 10 min. In response to IR 3, the Applicant stated that: *Disintegration data on registration stability batches as shown in Section 3.2.P.8.3 Stability Data (the data is extracted and presented in Table 3 and Table 4), is quite fast and it does not give meaningful quality control. Therefore, Shionogi would continue with dissolution test with revised acceptance criterion as included updated Section 3.2.P.5.1 Specifications.*

Table 3 **Stability Data in HDPE Bottle with Silica Gel Desiccant at 25°C/60% RH**

Test	Batch No.	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Disintegration (minutes, seconds) [a]	1211081	(b) (4)						
	1302009							
	1303011							

a. Mean of results for six tablets.

Table 4 **Stability Data (b) (4) at 25°C/60% RH**

Test	Batch No.	Initial	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Disintegration (minutes, seconds) [a]	1211081	(b) (4)						
	1302009							
	1303011							

a. Mean of results for six tablets.

However, based on our analysis of dissolution and disintegration results for all three batches at stability testing at 25°C/60% RH up to 48 hrs, the release of the tested batches at 10 min didn't

change significantly at different time periods of stability test, while the disintegration time of the tested stability batches (b) (4) months (Figure 6). Therefore, compared to dissolution test, disintegration time has a better discriminatory ability to detect the change in drug quality during stability test.

Figure 6A. Dissolution test and disintegration test results from stability data (HDPE Bottle) at 25°C/60% RH

(b) (4)

Figure 6B. Dissolution test and disintegration test results from stability data (b) (4) at 25°C/60% RH

(b) (4)

Therefore, another IR was conveyed to the Applicant on August 12, 2016:

FDA Request:

Based on our analysis of dissolution and disintegration results for all three batches under stability testing at 25°C/60% RH (Tables 3, 5, 7, 9,11,13 in Section 3.2.P.8.3), the disintegration test demonstrates a better discriminatory power compared to the dissolution test. The drug

release at 10 min didn't show significant difference in dissolution from (b) (4) under stability testing while there is a clear trend (b) (4) in disintegration time from (b) (4) under stability testing. Therefore, for quality control purpose, we recommend that in addition to the dissolution test, the disintegration test be implemented on release and stability, in accordance to ICH Guideline Q6A: Decision tree (b) (4).

On August 19, 2016, the Applicant responded that:

Shionogi will add Disintegration Test by USP <701> with acceptance criterion of NMT (b) (4) minutes to drug product specifications. This will be applied to release and stability testing.

Updated Sections 3.2.P.5.1 Specifications; 3.2.P.5.2 Analytical Procedures Summary; 3.2.P.5.2.10 Analytical Procedures - Disintegration; 3.2.P.8.2. Post-Approval Stability Protocol and Stability Commitment and 2.3.QOS – Drug Product are submitted.

However, as Table 3 and 4 submitted by the Applicant and Figure 6 above show, the mean disintegration time of all three batches at time (b) (4) of the stability test is in the range of (b) (4) seconds. Therefore, the proposed acceptance criterion for disintegration time of NMT (b) (4) minutes is too liberal.

In the IR conveyed to the Applicant on August 23, 2016, we recommended that:

Based on your disintegration data generated during stability test with a mean of around (b) (4) seconds (initial at release), your proposed acceptance criterion of (b) (4) min is considered too liberal. Therefore, we recommend an acceptance criterion of NMT (b) (4) min for disintegration test in drug product specifications. This will be applied to release and stability testing as a quality control of your drug product.

Revise accordingly in Sections 3.2.P.5.1 Specifications; 3.2.P.5.2 Analytical Procedures Summary; 3.2.P.5.2.10 Analytical Procedures - Disintegration; 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment and 2.3.QOS – Drug Product.

On August 29, 2016, the Applicant acknowledged the acceptance of NMT (b) (4) min as the disintegration specification. The revised acceptance criterion will apply to release and stability testing of the drug product. The Applicant updated Sections 3.2.P.5.1 Specifications; 3.2.P.5.6 Justification of Specification(s); and 2.3 Quality Overall Summary – Drug Product.

Note: The disintegration test method will be used for routine release and stability testing for drug product quality control purpose. However, the approved dissolution method should be employed for assessing the SUPAC changes.

Bridging of Formulations

Reviewer's Assessment:

In the first clinical trials, naldemedine oral solution / suspension containing 0.01 mg to 100 mg of naldemedine as free base has been used (Table 7).

Table 7. Components and Composition of Naldemedine Oral Solution/ Suspension

Naldemedine Solution / Suspension	0.01 mg [b]	0.03 mg [c]	0.1 mg	0.3 mg	1 mg	3 mg	10 mg	30 mg	100 mg
Components	Quantity per Dose (mg)								
Naldemedine Tosylate (as Naldemedine)	(b) (4)								
Hydroxypropyl Cellulose	(b) (4)								
Total									

a Only 100 mg dose is a suspension

b (b) (4)

c (b) (4)

Later in Phase 1 to Phase 2b studies, a (b) (4) film-coated tablet (tablet weight: (b) (4) mg, strength: 0.1 mg, 1 mg, 10 mg) was used. The tablet for Phase 3 clinical studies is a yellow, round shaped 6.5 mm in diameter film-coated tablet (tablet weight: 120 mg, strength: 0.2 mg). The to-be-marketed formulation is identical to the Phase 3 clinical study formulation. Components and composition of naldemedine tablets for phase 1 to phase 2b and phase 3 clinical studies and commercial (to-be-marketed) are shown in Table 8.

Table 8. Components and Composition of Naldemedine Tablets for Phase 1 to Phase 2b and Phase 3 Clinical Studies and Commercial (To-Be-Marketed)

Component	Composition (Amount (mg) per Tablet)			
	For Phase 1 to Phase 2b Clinical Study			For Phase 3 Clinical Studies and Commercial
	0.1 mg Tablet	1 mg Tablet	10 mg Tablet	0.2 mg Tablet
Naldemedine Tosylate (as naldemedine)	(b) (4)			0.26 (0.2)
D-Mannitol				(b) (4)
Croscarmellose Sodium				
Magnesium Stearate				
				(b) (4)
Hypromellose	(b) (4)			-
Talc				-
				(b) (4)

a The components and composition are described in Section 3.2.P.1.2.

b (b) (4)

As Table 7 shows, different strengths of oral solution formulations (b) (4)

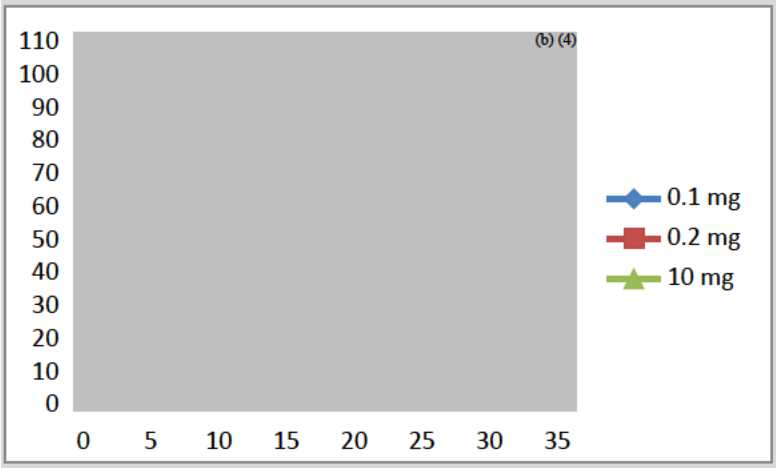
As Table 8 shows, different strengths of tablet formulation in Phase 1 and Phase 2b (b) (4).

Furthermore, based on clinical study 0824V9211, the C_{max} and AUC of naldemedine increased in an almost dose-proportional manner in the fasted state within the dose range from 0.1 mg to 100 mg when administered as an oral solution (0.1 to 30 mg) or suspension (100 mg).

The 10 mg oral solution formulation was bridged to Phase 1 and Phase 2b 10 mg tablet formulation by BA/BE Study 0909V9212. The lower bound of the 90% CI for the GMR (Tablet/Solution) of C_{max} for naldemedine (0.909 (0.775-1.07)) fell slightly outside of the bound for bioequivalence (0.8000 to 1.2500), while AUC met the BE criteria. However, the differences in C_{max} values as stated by the Applicant were not statistically significantly different between the tablet and the solution formulations. The Phase 1 and Phase 2b 0.1 mg tablet was bridged to Phase 3 and TBM 0.2 mg tablet by BA/BE study 1311V921A. The upper bound of the 90% CI for the GMR (Phase 3 Tablet/Phase 2 Tablet) of C_{max} for naldemedine (1.1328(1.0183-1.2602)) fell slightly outside of the bound for bioequivalence (0.8000 to 1.2500), while AUC met the BE criteria. The differences in C_{max} and AUC values were small (13% and 4%, respectively) and were not considered clinically meaningful between 0.2 mg and 0.1 mg tablets as stated by the Applicant. The review and acceptance of these two BA/BE studies will be determined by reviewer in Office of Clinical Pharmacology and clinical team.

Figure 7 shows the dissolution profiles of Phase 1 and Phase 2b 0.1 mg or 10 mg tablets and Phase 3 or TBM 0.2 mg tablet. The dissolution profile of 10 mg tablet is adapted from Figure 3 (T8Y25). The release from both tablet formulations is very fast and reaches more than (b) (4)% within 10 min, and the dissolution profiles are superimposed. Furthermore, since the drug release is more than (b) (4)% within 10 min (Table 5, Figure 3, and Figure 7), dissolution is not the rate limit step for drug absorption and f2 calculation is not needed to demonstrate the similarity in dissolution profiles.. Based on the dissolution similarity and linear PK of naldemedine, the similarity in PK from BA/BE study between 0.1 mg and 0.2 mg tablets could be extrapolated to other strengths of Phase 1 and Phase 2b tablets.

Figure 7. Comparative dissolution profiles of Phase 1 and Phase 2b 0.1 mg and 10 mg tablets and Phase 3 or TBM 0.2 mg tablet



Overall, Phase 1 and Phase 2b tablet formulation is considered bridged to Phase 3 and TBM tablet formulation pending on the acceptance of BA/BE studies by clinical pharmacology reviewer.

List of Deficiencies: N/A

From Biopharmaceutics perspective, NDA 208854 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date: Peng (Vincent) Duan, Ph.D. 10/6/2016

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

I concur. 10/19/16

Tien-Mien Chen, Ph.D.

Acting Biopharm lead; DS/ONDP/OPQ

Tien Mien Chen

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Peng Duan

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ATTACHMENT I: Method Validation Summary

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Sara Ibrahim
Office of OMPT/CDER/OPQ/ONDP/DNDPI
E-mail Address:sarah.ibrahim@fda.hhs.gov
Phone: (240)-402-6154

FROM: FDA
Division of Pharmaceutical Analysis
Michael E. Hadwiger, Ph.D., MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314)-539-3811

Through: David Keire, Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA
Phone: (314) 539-3850

SUBJECT: Methods Validation Report Summary

Application Number: NDA 208854

Name of Product: Symproic™ (Naldemedine Tosylate tablet)

Applicant: SHIONOGI INC

Applicant's Contact Person: Ting Chen

Address: 300 Campus Drive Florham Park, NJ 07932

Telephone: 973-966-6900 Email: tchen@shionogi.com

Date Methods Validation Consult Request Form Received by DPA: 4/14/2016

Date Methods Validation Package Received by DPA: 4/14/2016

Date Samples Received by DPA: 6/24/2016 and 8/16/2016

Date Analytical Completed by DPA: 9/21/2016

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Avenue
St. Louis, Missouri 63110
Telephone (314) 539-3850
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Date: 09/22/2016

To: Sara Ibrahim, OMPT/CDER/OPQ/ONDP/DNDPI

Through: David Keire, Ph.D., CDER/OPQ/OTR/DPA, Lab Chief, Branch I

From: Cindy Ngo, CDER/OPQ/OTR/DPA

Subject: Method Validation for NDA/ANDA 208854: Symproic™ (Naldemedine Tosylate tablet)

The following methods were (1) verified and found acceptable for quality control and regulatory purposes:

1. 3.2. S.4.2.4 Analytical Procedures-Related Substances by HPLC, Shionogi, page 1-5.
2. 3.2. S.4.2.2 Analytical Procedures - Identification of Naldemedine tosylate by ultraviolet spectroscopy, Shionogi, Page 1-1.
3. 3.2. S.4.2.3 Analytical Procedures - Identification of Naldemedine tosylate by Infrared spectroscopy, Shionogi, Page 1-1.
4. 3.2. S.4.2.8 Analytical Procedures- Assay for Naldemedine drug substance, Shionogi, page 1-3.
5. 3.2. P.5.2.2 Analytical Procedures - Identification by Ultraviolet Spectroscopy of Naldemedine tablets 0.2 mg, Shionogi, Page 1-1.
6. 3.2. P.5.2.3 Analytical Procedures - Related Substances 1 by HPLC, Naldemedine tablets 0.2 mg Shionogi, Page 1-4.
7. 3.2. P.5.2.4 Analytical Procedures - Related Substances 2 by HPLC, Naldemedine tablets 0.2 mg Shionogi, Page 1-4.
8. 3.2. P.5.2.7 Analytical Procedures – Dissolution for Naldemedine tablets 0.2 mg Shionogi, Page 1-4.
9. 3.2. P.5.2.8 Analytical Procedures – Assay for Naldemedine tablets 0.2 mg Shionogi, Page 1-3

Link to analyst worksheets and data:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880dc122a

Summary of Analysis:

1) **3.2. S.4.2.4 Analytical Procedures-Related Substances by HPLC, Shionogi, page 1-5.**

RRT	Name	Average (3) % Impurity	Specification %	Pass/Fail
			(b) (4)	Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass

LT (b) (4)% - Report only for impurity greater than or equal to (b) (4)%, except (b) (4)

NMT = No more than
LT = Less than

2) **3.2. S.4.2.2 Analytical Procedures - Identification of Naldemedine tosylate by ultraviolet spectroscopy, Shionogi, page 1-1.**

UV spectrum of the sample solution has similar intensities of absorption at the same wave lengths with the spectrum of the Naldemedine reference standard solution.

3) **3.2. S.4.2.3 Analytical Procedures - Identification of Naldemedine tosylate by Infrared spectroscopy, Shionogi, page 1-1.**

The sample and Naldemedine reference standard spectra exhibit similar intensities of absorption at the same wave numbers.

4) **Q3.2. S.4.2.8 Analytical Procedures- Assay for Naldemedine drug substance, Shionogi, page 1-3.**

	% of Naldemedine	Specification	Pass/Fail
Average (3)	(b) (4)	(b) (4)%	Pass

5) **3.2. P.5.2.2 Analytical Procedures - Identification by Ultraviolet Spectroscopy of Naldemedine tablets 0.2 mg, Shionogi, Page 1-1.**

The UV spectrum of Naldemedine obtained from the sample solution is identical to the UV spectrum of Naldemedine obtained from the standard solution in the range of (b) (4)nm with respect to their maxima.

6) **3.2. P.5.2.3 Analytical Procedures - Related Substances 1 by HPLC, Naldemedine tablets 0.2 mg Shionogi, Page 1-4.**

Summary for the % Related substance eluting after (b) (4)
Report only for impurity is greater than or equal to (b) (4)%

RRT	Compound name	Average (3) of % Impurity	Specification	Pass/Fail
(b) (4)			(b) (4)	Pass
	Total % Impurities			Pass

7) **3.2. P.5.2.4 Analytical Procedures - Related Substances 2 by HPLC, Naldemedine tablets 0.2 mg Shionogi, Page 1-4.**

Report only for impurity is greater than or equal to (b) (4)%	Compound name	Average (3)	Specification	Pass/Fail
(b) (4) RRT	(b) (4)		(b) (4)	Pass
				Pass
	Total % Impurities			Pass

Summary for the % Related substance eluting before (b) (4)

8) **3.2. P.5.2.7 Analytical Procedures – Dissolution for Naldemedine tablets 0.2 mg Shionogi, Page 1-4.**

Vessel #	Naldemedine peak Area	% Release
Vessel 1		(b) (4)
Vessel 2		
Vessel 3		
Vessel 4		
Vessel 5		
Vessel 6		
	Average	98.9
	Min	97.9
	Max	100.0

Q value for each vessel after (b) (4) minutes was greater than (b) (4)% of declared content, so the sample met the specification.

9) **3.2. P.5.2.8 Analytical Procedures – Assay Naldemedine tablets 0.2 mg Shionogi, Page 1-3.**

	% of Naldemedine	Specification	Pass/Fail
Average (3)	(b) (4)	(b) (4)%	Pass

ATTACHMENT II: Risk Assessment

Initial Risk Assessment for NDA 208854 Symproic (naldemedine) tablets, for oral use

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
tablet Appearance	Tablet chipping. Blister sealing and moisture	M to L	During the tablet manufacturing process (b) (4)	The registration batches met the appearance specification. During the stability testing no (b) (4) DP deterioration was found. Low to None	None
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	During manufacturing process development critical steps were identified and in process controls (IPC) such as (b) (4) were instituted for a robust manufacturing process and to constistantly produce quality DP. Assay is determined by a validated HPLC 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 DP specification at release and on stability. The impurities are assessed by validated HPLC methods.	Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The (b) (4) of the DS is controlled. During manufacturing the DP quality is controlled by IPC including (b) (4) Dissolution is also controlled by DP specification.	Low to None	None

ATTACHMENT III: List of Deficiencies for Complete Response

A. Labeling Deficiencies

- The labeling is not finalized yet.

OVERALL ASSESSMENT AND SIGNATURES:

From the quality perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6).

Application Technical Lead Name and Date:

Hitesh Shroff
Division of New Products II, Branch V
November 22, 2016

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: 2016.11.28 13:07:53 -05'00'

1 Document History

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: **This process will be reviewed approximately 150 days from date issued (February 18, 2016).**
Version	**Summary of Changes** **Date Issued**
03	Content update 02/18/2016