CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213478Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 14, 2021
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name)/Dosage Form and Route:	HYFTOR (sirolimus topical gel)
Application Type/Number:	NDA 213478
Applicant:	Nobelpharma Co., Ltd. c/o Dunn Regulatory Associates, LLC

1 INTRODUCTION

On December 23, 2020, Nobelpharma Co., Ltd. c/o Dunn Regulatory Associates LLC, submitted for the Agency's review a Class 2 Resubmission of their original New Drug Application (NDA) 213478 for HYFTOR (sirolimus topical gel) in response to a Complete Response (CR) letter issued by FDA on August 13, 2020. The proposed indication for HYFTOR (sirolimus topical gel) is for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and (b) (4) We note that the proposed proprietary name HYFTOR was found to be conditionally acceptable by the Division of Medication Error Prevention and Risk Management on March 18, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 8, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for HYFTOR (sirolimus topical gel). The proposed MG was converted to a Patient Package Insert (PPI) by DDD on June 18, 2020.

The HYFTOR (sirolimus topical gel) PPI from the DMPP and OPDP collaborative review dated July 17, 2020 was used for this review, at the request of DDD on June 4, 2021.

2 MATERIAL REVIEWED

- Draft HYFTOR (sirolimus topical gel) MG received on December 23, 2020.
- DMPP and OPDP collaborative review of HYFTOR (sirolimus topical gel) PPI dated July 17, 2020, reviewed and revised by the Review Division, and received by DMPP and OPDP on June 2, 2021.
- Draft HYFTOR (sirolimus topical gel) Prescribing Information (PI) received on December 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 2, 2021.
- Approved RAPAMUNE (sirolimus) labeling dated January 2, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
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LAURIE J BUONACCORSI
06/14/2021 02:59:19 PM

SHARON R MILLS
06/14/2021 03:15:38 PM

LASHAWN M GRIFFITHS
06/14/2021 03:36:11 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 4, 2021

To: Kevin Clark, MD/Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Gordana Diglisic, MD/Clinical Team Lead, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for HYFTOR™ (sirolimus) topical gel

NDA: 213478

In response to DDD's consult request dated January 8, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the NDA resubmission for HYFTOR™ (sirolimus) topical gel.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on June 2, 2021.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 26, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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CONTAINER/CARTON COMMENTS

The established name should be at least half as large as the letters comprising the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The proprietary name is more than twice the size of the established name. In addition, the light color and font type used for the established name lacks prominence compared to the colorful and bolded font of the proprietary name. We recommend revision. Please apply this comment to all container and carton labeling.

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/s/

LAURIE J BUONACCORSI
06/04/2021 11:32:38 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 11, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213478
Product Name and Strength:	Hyftor (sirolimus topical gel), 0.2%
Applicant/Sponsor Name:	Nobelpharma Co., Ltd.
OSE RCM #:	2020-327-3
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 8, 2021 for Hyftor. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Hyftor (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note that the Applicant submitted two different versions of the container label and carton labeling (b) (4) We defer to the Office of Product Quality (OPQ) to evaluate the Applicant's proposal to note the use of alcohol 51%.

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel M. Label and Labeling Review MEMO for Hyftor (NDA 213478). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 24. RCM No.: 2020-327-2.

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/s/

MADHURI R PATEL
03/11/2021 01:54:03 PM

SEVAN H KOLEJIAN
03/11/2021 01:58:28 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 24, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213478
Product Name and Strength:	Hyftor (sirolimus topical gel), 0.2%
Applicant/Sponsor Name:	Nobelpharma Co., Ltd.
OSE RCM #:	2020-327-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

NDA 213478 received a Complete Response (CR) on August 13, 2020 for product quality deficiencies. We previously reviewed the label and labeling and provided recommendations.[a,b] This MEMO evaluates the revised Prescribing Information (PI), Medication Guide (MG), container label and carton labeling received on December 23, 2020 for Hyftor as part of the Class 2 Resubmission package. Division of Dermatology and Dentistry (DDD) requested that we review the revised PI, MG, container label and carton labeling for Hyftor (Appendix A) to determine if they are acceptable from a medication error perspective.

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that since our previous review, the NDC number has been added to the container label and carton labeling. We also note the carton labeling no longer shows the 2D data matrix with the expiration date next to it. The revised MG is acceptable from a medication error perspective. However, we note that the PI can be improved to facilitate product identification and the container label and carton labeling can be improved to increase prominence of

[a] Patel M. Label and Labeling Review for Hyftor (NDA 213478). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 21. RCM No.: 2020-327.
[b] Patel M. Labeling Review MEMO for Hyftor (NDA 213478). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 06. RCM No.: 2020-327-1.

important information (e.g. established name, [redacted], storage conditions) and to prevent wrong dose errors.

3 CONCLUSION

The revised MG is acceptable from a medication error perspective. However, we note that the PI can be improved to facilitate product identification and the container label and carton labeling can be improved to increase the prominence of important information and prevent wrong dose errors. We provide recommendations below in Section 3.1 for the Division and Section 3.2 for the Applicant to address our concerns.

3.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

a. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-XX). Replace this NDC placeholder with the actual NDC.

b. We note the net quantity is not included (i.e. 10 g). Consider adding this information next to "aluminum tube".

3.2 RECOMMENDATIONS FOR NOBELPHARMA CO., LTD.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Label and Carton Labeling)

a. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

b. The strength statement, 0.2 %, appears far away from the product name and dosage form. To facilitate product identification, we recommend relocating the strength statement to appear closer to product name and dosage form statement.

c. Add the statement [redacted] or similar statement prominently displayed on the Principal Display Panel (PDP) in accordance with 21 CFR 208.24(d).

d. To ensure consistency with the Prescribing Information, revise the statement, [redacted] to read [redacted] If space is limited, the statement may read "Recommended Dosage and Administration: See prescribing information."

e. Revise and bold the statement "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

B. Container Label

a. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Carton Labeling

a. We recommend that a hyphen or a space be used to separate the portions of the expiration date.
b. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 2 mg/g instead of 2mg/g).
c. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The human-readable product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.

NDC: [insert product's NDC]
SERIAL: [insert product's serial number]
LOT: [insert product's lot number]
EXP: [insert product's expiration date]

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[c] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

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MADHURI R PATEL
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SEVAN H KOLEJIAN
02/24/2021 03:55:27 PM

MEMORANDUM

REVIEW OF REVISED AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 6, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213478
Product Name and Strength:	Hyftor (sirolimus) gel, 0.2%
Applicant/Sponsor Name:	Nobelpharma Co., Ltd.
OSE RCM #:	2020-327-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

This memorandum is an addendum to our previous Label and Labeling Review.[a] Since our previous label and labeling review, the proposed dosing for Hyftor gel has been revised from (b) (4) to a specific maximum daily dose of 600 mg (2 cm) for ages 6-11 years and 800 mg (2.5 cm) for 12 years of age and older. We wanted to understand the risks associated with medication errors related to revised dosing for Hyftor gel. As such, we discussed the concern with the Division of Dermatology and Dentistry (DDD) clinical and clinical pharmacology team. Per DDD, (b) (4) of Hyftor gel is acceptable from a clinical perspective. Hence for this product, DMEPA finds the revised dosing information and the Patient Labeling Team (PLT) proposal to add a statement to the Patient Package Insert (PPI) regarding healthcare professionals showing the patient how to correctly measure, acceptable.

2 CONCLUSION

We find the proposed revision regarding the dosing to the Prescribing Information (PI) and Patient Package Insert (PPI) acceptable from a medication error perspective.

[a] Patel, M. Label and Labeling Review for Hyftor (NDA 213478). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 21. RCM No.: 2020-327.

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MADHURI R PATEL
08/06/2020 09:13:06 AM

SEVAN H KOLEJIAN
08/06/2020 10:53:29 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 17, 2020
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name)/Dosage Form and Route:	HYFTOR (sirolimus) Topical Gel
Application Type/Number:	NDA 213478
Applicant:	Nobelpharma Co., Ltd.

1 INTRODUCTION

On February 18, 2020, Nobelpharma Co., Ltd. submitted for the Agency's review an original New Drug Application (NDA) 213478 for HYFTOR (sirolimus) Topical Gel. The proposed indication for HYFTOR (sirolimus) Topical Gel is the treatment of facial angiofibroma associated with tuberous sclerosis in adults and (b) (4). The Applicant originally submitted a Medication Guide (MG) with their NDA, which was converted to a Patient Package Insert (PPI) by the Division of Dermatology and Dentistry (DDD) on June 18, 2020.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by DDD on March 6, 2020, for DMPP and OPDP to review the Applicant's proposed MG for HYFTOR (sirolimus) Topical Gel.

2 MATERIAL REVIEWED

- Draft HYFTOR (sirolimus) Topical Gel MG received on February 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 7, 2020.
- Draft HYFTOR (sirolimus) Topical Gel Prescribing Information (PI) received on February 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 7, 2020.
- Approved RAPAMUNE (sirolimus) labeling dated January 2, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER
07/17/2020 01:52:11 PM

LASHAWN M GRIFFITHS
07/17/2020 01:53:07 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 15, 2020

To: Kevin Clark, MD/Clinical Reviewer, M.D.
Division of Dermatology and Dentistry (DDD)

Strother Dixon, Regulatory Project Manager, (DDD)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for HYFTOR™ (sirolimus) topical gel

NDA: 213478

In response to DDD's consult request dated March 6, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for HYFTOR™ (sirolimus) topical gel.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on July 7, 2020.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 18, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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CONTAINER/CARTON COMMENTS

1. There is intervening matter between the proprietary and established name. The proprietary and established names should appear together, without any intervening written, printed, or graphic matter, which may detract, obfuscate, or de-emphasize the established name, or obscure the relationship between the proprietary and established names. (b) (4) constitute intervening matter that detracts from and de-emphasizes the established name. We recommend deletion. Please apply this comment to all container and carton labeling.

2. The established name should be at least half as large as the letters comprising the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The proprietary name is more than twice the size of the established name. We recommend revision. Please apply this comment to all container and carton labeling.

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/s/

LAURIE J BUONACCORSI
07/15/2020 09:47:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: July 7, 2020 **Date consulted:** April 15, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Strother Dixon, Regulatory Project Manager (RPM)
Division of Dermatology and Dentistry (DDD)

Drug: Hyftor (sirolimus) topical gel, 0.2%

NDA: 213478

Applicant: Nobelpharma Co., Ltd

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of angiofibroma associated with tuberous sclerosis in adults and (b) (4)

Materials Reviewed:

- NDA 213478 submission dated February 18, 2020.
- Applicant's response to information request (IR) dated April 8, 2020.

Consult Question: DDD requests "Maternal Health review of the PLLR labeling"

INTRODUCTION

On February 18, 2020, the applicant, Nobelpharma Co., Ltd submitted a new drug application (NDA 213478) for Hyftor (sirolimus) topical gel, 0.2% via the 505(b)(2) regulatory pathway. On April 15, 2020, the Division of Dermatology and Dentistry consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indication for Hyftor (sirolimus) topical gel, 0.2% is the treatment of angiofibroma associated with tuberous sclerosis (TS) in adults and (b) (4) Orphan designation was granted on May 17, 2017.
- The applicant is relying on the FDA's finding of safety and effectiveness for Rapamune (sirolimus) tablets (NDA 021110) as the listed drug relied upon.
- Sirolimus received initial U.S. market approval in 1999.
- On April 1, 2020, the Agency sent the applicant an information request (IR) to provide a review of available information regarding use of sirolimus gel in pregnant women, lactating women, and females and males of reproductive potential from the clinical development program.
- On April 8, 2020, the applicant submitted the requested information.

Drug Characteristics[1]

- *Drug class*: mammalian target of rapamycin (mTOR) inhibitor.
- *Mechanism of action (MOA):* the MOA in the treatment of angiofibroma associated with TS is unknown. TS is associated with genetic defects in TSC1 and TSC2 leading to the activation of mTOR. Sirolimus inhibits mTOR activation.
- *Dosage and administration*: topical gel applied to the skin of the face affected with angiofibroma twice daily in the morning and at bedtime. The maximum daily dose should not exceed 600 mg (age 6 to 11 years) and 800 mg (age 12 years and older). If symptoms do not improve within 12 weeks of treatment, re-evaluate the need for continuing Hyftor gel.
- *Dosage forms and strengths*: 0.2% gel in 10-gram tubes. Each gram contains 2 mg of sirolimus.
- *Molecular weight*: 914.19 Daltons
- *Absorption:* Following 12 weeks of treatment with Hyftor in adult and pediatric subjects aged 6 years and older, sirolimus blood concentrations ranged from undetectable to 0.50 ng/mL after multiple doses of Hyftor in the Phase 3 trial. Periodic blood samples were obtained in the (b) (4) study and the maximum sirolimus concentration measured at any time in adult subjects was 3.27 ng/mL and the maximum sirolimus concentration measured at any time in pediatric subjects was 1.80 ng/mL
- *Adverse reactions*: dry skin, application site irritation, acne, pruritis, eye irritation, erythema, dermatitis acneiform, and contact dermatitis.

[1] Hyftor topical gel, 0.2% (NDA 213478) proposed package insert

Reviewer's Comment
At the June 17, 2020 labeling meeting, the Clinical Pharmacology Team noted their disagreement with the applicant's proposed labeling in subsection 8.1 and 8.2 that (b) (4) *The Clinical Pharmacology Team noted that systemic levels of sirolimus were quantifiable in 44% to 78% of all subjects following topical administration on a ng/mL measurement unit. The maximum sirolimus concentration measured at any time in adult subjects following topical administration was 3.27 ng/mL which is 5-fold lower than the maximum concentration following the 2 mg oral sirolimus dose. Further, the Clinical Pharmacology Team noted the pharmacokinetic (PK) sampling data was so sparse that an AUC could not be calculated.*

Current State of the Labeling[2]
Rapamune (sirolimus) tablets (NDA 021110), the listed drug relied upon, currently approved labeling is in the Physician Labeling Rule (PLR) and PLLR format.

- *5.15 Embryo-Fetal Toxicity*:
    - Based on animal studies and the mechanism of action, Rapamune can cause fetal harm when administered to a pregnant woman. In animal studies, sirolimus caused embryo-fetal toxicity when administered during the period of organogenesis at maternal exposures that were equal to or less than human exposures at the recommended lowest starting dose. Advise women of the potential risk to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using Rapamune and for 12 weeks after ending treatment.

- *5.16 Male Infertility*
    - Azoospermia or oligospermia may be observed. Rapamune is an anti-proliferative drug and affects rapidly dividing cells like the germ cells.

- *6.7 Postmarketing Experience*
    - The following adverse reactions have been identified during post-approval use of Rapamune in transplant patients.
        - Urogenital-ovarian cysts, menstrual disorders (including amenorrhea and menorrhagia). Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases.

- *8.1 Pregnancy Risk Summary*
    - Based on animal studies and the mechanism of action, Rapamune can cause fetal harm when administered to a pregnant woman. There are limited data on the use of sirolimus during pregnancy; however, these data are insufficient to inform a drug-associated risk of adverse developmental

[2] Rapamune oral tablets (NDA 021110) currently approved labeling from 1/02/20. Drugs@FDA

outcomes. In animal studies, sirolimus was embryo/fetotoxic in rats at sub-therapeutic doses. Advise pregnant women of the potential risk to a fetus.

- *8.2 Lactation*
  - It is not known whether sirolimus is present in human milk. There are no data on its effects on the breastfed infant or milk production. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Sirolimus is present in the milk of lactating rats. There is a potential for serious adverse effects from sirolimus in breastfed infants based on mechanism of action. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rapamune and any potential adverse effects on the breastfed child from Rapamune.

- *8.3 Females and Males of Reproductive Potential*
  - Contraception: females should not be pregnant or become pregnant while receiving Rapamune. Advise females of reproductive potential that animal studies have shown Rapamune to be harmful to the developing fetus. Females of reproductive potential are recommended to use a highly effective contraceptive method. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped.
  - Infertility: Based on clinical findings and findings in animals, male and female fertility may be compromised by the treatment with Rapamune. Ovarian cysts and menstrual disorders (including amenorrhea and menorrhagia) have been reported in females with use of Rapamune. Azoospermia has been reported in males with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases.

- *17 Patient Counseling*
  - Pregnancy and Lactation: Advise female patients of reproductive potential to avoid becoming pregnant throughout treatment and for 12 weeks after Rapamune therapy has stopped. Rapamune can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to her fetus. Before making a decision to breastfeed, inform the patient that the effects of breastfeeding in infants while taking this drug are unknown, but there is a potential for serious adverse effects.
  - Infertility: Inform male and female patients that Rapamune may impair fertility.

DATA REVIEW
PREGNANCY
Nonclinical Experience
Animal reproduction studies have not been conducted with Hyftor gel. In an animal reproduction study, oral administration of 0.5 mg/kg/day sirolimus caused embryofetal lethality in pregnant rats when administered during the period of organogenesis. The

available data do not allow the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of Hyftor gel. For additional information, the reader is referred to Nonclinical Review by Jill Merrill, PhD.

Reviewer's Comment
On June 26, 2020, DPMH met with the DDD Clinical, Nonclinical, and Clinical Pharmacology Review Teams to discuss the clinical relevance of the animal reproduction studies with oral sirolimus to Hyftor gel. The Clinical Team noted the threshold sirolimus blood level at which systemic adverse effects may occur is unknown. DPMH explored with the DDD Review Team whether or not the no observed adverse effect level (NOAEL) in animal reproduction studies with oral sirolimus may able to inform a safety margin with topical sirolimus. However, the Clinical Pharmacology Team noted (as described above) that PK sampling was too sparse to allow AUC calculation. Further, the Nonclinical Team noted that maximum concentration (Cmax) cannot be used for calculating exposure multiples for a repeat dose topical drug, rather AUC is needed. Thus, the Clinical Review Team determined the Warnings and Precautions for oral sirolimus (such as Embryo-Fetal Toxicity and Male Infertility relevant to PLLR) will be included in Hyftor gel labeling as class labeling.

Clinical Experience
Clinical Trials
Pregnant women were excluded from clinical trials with sirolimus gel, 0.2%. The applicant stated there have been 3 reports of pregnancy from the investigators as follows:

1. (b) (6) female treated with sirolimus gel for 78 days and discontinued treatment at 13 weeks gestation. *Outcome*: normal delivery of a healthy child.
2. (b) (6) female treated with sirolimus gel for 116 days and discontinued treatment at 4 weeks gestation. *Outcome*: ongoing (due date (b) (6)).
3. (b) (6) female treated with sirolimus gel for 126 days and discontinued treatment at 8 weeks gestation. *Outcome*: spontaneous abortion at 17 weeks gestation. The spontaneous abortion was deemed to be due to cervical insufficiency and unrelated to sirolimus gel. The patient had a history of 4 prior pregnancies that resulted in no live births prior to treatment with sirolimus.

Applicant's Review of the Published Literature
The applicant did not perform a published literature search related to sirolimus use during pregnancy.

DPMH's Review of the Published Literature
This Reviewer performed a literature search in PubMed, Embase, Micromedex[3], TERIS[4], Reprotox[5], and Briggs[6] for relevant articles related to sirolimus use during pregnancy.

[3]Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 6/10/20
[4]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 6/10/20.
[5]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 6/10/20.
[6] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide , 9th Ed. 2011.

Search terms included: “topical sirolimus” OR “sirolimus” AND “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” OR “miscarriage.”

No relevant publications were identified describing the use of topical sirolimus during pregnancy. However, the following relevant publications were identified describing the use of oral sirolimus during pregnancy:

- The **Reprotox** summary states “based on studies in rats, oral sirolimus therapy may decrease fetal viability and growth. There are a few case reports of normal development after exposure during early pregnancy.” The following clinical articles are cited:
    - Case report of a women who became pregnancy while on oral sirolimus for a liver transplant. Sirolimus was stopped at 6 weeks gestation and tacrolimus was substituted. A healthy infant was delivered at term.[7]
    - In a report from the National Transplantation Pregnancy Registry,[8] there were 6 women exposed during early pregnancy to oral sirolimus.
        - Three pregnancies miscarried in the 1st trimester.
        - The other three pregnancies resulted in babies without birth defects. Two of theses three children were delivered prematurely, which the authors associated with pregnancy in transplant recipients in general.
        - There was an additional patient who was exposed to mycofenolate mofetil early in pregnancy which was switched to sirolimus at 24 weeks and the outcome was preterm delivery with microtia and cleft lip/palate; however, based on the timing of exposure, the malformations were not attributed to sirolimus.
    - A case report describes a woman on oral sirolimus 2mg daily throughout pregnancy for the treatment of lymphangioleiomyomatosis who delivered a healthy infant preterm at 32 weeks gestation, and the child showed normal development at 7 months of age.[9]
    - A case report of a 21-week fetus with cardiac rhabdomyomas who was successfully treated with oral sirolimus therapy of the mother.[10] Infant treatment was continued postnatally and at 9 months of age the infant was developing normally.

- **Shephard’s**[11] overview notes the following regarding the use of oral sirolimus during pregnancy:

[7] Jankowska I, et al. Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. Transplant Proc. 2004;36(10):3232-3233.
[8] Sifontis NM, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation. 2006;82(12):1698-1702.
[9] Faehling M, et al. Long-term stable lung function and second uncomplicated pregnancy on sirolimus in lymphangioleiomyomatosis (LAM). Sarcoidosis Vasc Diffuse Lung Dis 32(3): 259-264. 2015.
[10] Barnes BT, et al. 2018. Maternal sirolimus therapy for fetal cardiac rhabdomyomas. 378: 1844-1845.
[11] 2020 Shepard's: A Catalog of Teratogenic Agents, accessed 6/11/20.
www micromedexsolutions.com/micromedex2/librarian/CS/7E8C45/ND_PR/evidencexpert/ND_P/evidenc

- A series reported by the National Transplantation Pregnancy Registry includes 3 infants with major congenital anomalies among 19 liveborn infants of women who were treated with oral sirolimus during pregnancy.[12,13,14,15] One infant had tetralogy of Fallot and the other infant had a Dandy-Walker malformation. The third infant had cleft lip/palate and microtia (this is the same case described above in which sirolimus was started at the 24th week of gestation following the mother's use of mycophenolate mofetil early in pregnancy, and the observed anomalies were not attributed to oral sirolimus exposure).
- Five normal infants whose mothers were treated with oral sirolimus early in pregnancy have been reported in the literature.[16,17,18,19,20] Treatment with oral sirolimus was continued throughout the entire pregnancy in 2 of the mothers.[21,22]

- **TERIS** states the magnitude of teratogenic risk to a child born after exposure to sirolimus during gestation is "undetermined" based on "limited" quality and quantity of data on which the risk estimate is based. "Although the teratogenic risk associated with maternal sirolimus treatment during pregnancy is unknown, this risk may be substantial because sirolimus suppresses the mTOR cellular signaling pathway, which is important in embryogenesis.[23]" The relevant literature cited is the same as that already described above under **Shepard's**.

- The **Micromedex** pregnancy rating for oral sirolimus is "fetal risk cannot be ruled out. Available evidence is inconclusive or is inadequate for determining fetal risk

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[12] Armenti VT, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin. Transpl. 131-141, 2003.

[13] Sifontis NM, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 82(12):1698-1702, 2006.

[14] Coscia LA, et al.: Immunosuppressive drugs and fetal outcome. Best Pract. Res. Clin. Obstet. Gynaecol. 28(8):1174-1187, 2014.

[15] Moritz MJ, et al.: Transplant Pregnancy Registry International: 2016 Annual Report. Philadelphia, Pa.: Gift of Life Institute, June 2017. Available at: TransplantPregnancyRegistry.org

[16] Jankowska I, et al.: Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. Transplant. Proc. 36(10):3232-3233, 2004.

[17] Guardia O, et al. Pregnancy under sirolimus-based immunosuppression. Transplantation 81(4):636, 2006.

[18] Chu S, et al. Sirolimus used during pregnancy in a living related renal transplant recipient: a case report. Transplant. Proc. 40(7):2446-2448, 2008.

[19] Framarino dei Malatesta M, et al.: Successful pregnancy in a living-related kidney transplant recipient who received sirolimus throughout the whole gestation. Transplantation 91(9):e69-e71, 2011.

[20] Faehling M, et al: Long-term stable lung function and second uncomplicated pregnancy on sirolimus in lymphangioleiomyomatosis (LAM). Sarcoidosis Vasc. Diffuse Lung Dis. 32(3): 259-264, 2015

[21] Framarino dei Malatesta M, et al: Successful pregnancy in a living-related kidney transplant recipient who received sirolimus throughout the whole gestation. Transplantation 91(9):e69-e71, 2011

[22] Faehling M, et al.: Long-term stable lung function and second uncomplicated pregnancy on sirolimus in lymphangioleiomyomatosis (LAM). Sarcoidosis Vasc. Diffuse Lung Dis. 32(3): 259-264, 2015

[23] Hwang M, et al: The mTOR signaling network: insights from its role during embryonic development. Curr Med Chem 15(12):1192-1208, 2008

when used in pregnant women or women of childbearing potential. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during pregnancy."

- **Briggs** pregnancy recommendation for oral sirolimus is "limited human data-animal data suggest moderate risk." The authors state, "only a few reports of exposure to oral sirolimus in human pregnancy have been located. The animal reproduction data suggest a potential for toxicity, but not for teratogenicity. The very limited human pregnancy experience prevents a full assessment of the risk."

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with Hyftor gel. After oral administration, sirolimus was present in the milk of lactating rats. For additional information, the reader is referred to the Nonclinical Review by Jill Merrill, PhD.

Clinical Experience

Clinical Trials

Lactating women were excluded from clinical trials with sirolimus gel, 0.2%. The applicant stated there are no available data on the effects of sirolimus gel on lactation.

Applicant's Review of the Published Literature

The applicant did not perform a published literature search related to sirolimus use in lactating women.

DPMH's Review of the Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*[24], Micromedex[5], Reprotox[7], PubMed, and Embase for articles relevant to sirolimus use during lactation. Search terms included: "topical sirolimus" OR "sirolimus" AND "lactation" OR "breastfeeding."

No relevant publications were identified describing the use of topical sirolimus during lactation. However, the following relevant publications were identified describing the use of oral sirolimus during lactation:

- The **LactMed** summary of use during lactation states "because almost no information is available on the use of sirolimus during breastfeeding, an alternative drug may be preferred, especially while nursing a newborn or preterm infant."
    - *Maternal and infant drug levels:* No relevant published information found.
    - *Effects in the breastfed infants:* One infant was reported breastfed (extent not stated) during maternal therapy with sirolimus, tacrolimus, and

[24] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

prednisone in unspecified dosages following a kidney-pancreas transplant. No serious side effects were reported in the breastfed infant.[25]

- *Effects on lactation and breastmilk:* No relevant published information found.

- *Medications and Mother's Milk* rates sirolimus as L4-No Data-Possibly Hazardous. The author, Thomas Hale, notes "sirolimus is an immunosuppressant sometimes used in combination with cyclosporine in renal transplants. No data are available on its transfer to human milk. Average plasma levels are quite low (264 ng x hr/mL) and the drug is strongly attached to cellular component and plasma levels are low. It is not likely it will penetrate milk in levels that are sufficient. However, it is a potential inhibitor of the enzyme 70K S6 kinase, which is stimulated in breast tissue by prolactin. This agent, in rodent mammary tissue, strongly inhibits milk component production. It could potentially suppress milk production in lactating mothers and caution is recommended."

- **Briggs** breastfeeding recommendation is "no human data-potential toxicity." The authors note no reports describing the use of sirolimus during human lactation have been located. The molecular weight (about 914 Daltons) and the prolonged half-life (about 62 hours) suggest that the drug will be excreted into breast milk. The effect of this potential exposure on a nursing infant is unknown, but consideration should be given to the carcinogenic properties of sirolimus, especially with long-term exposures. A 2002 review concluded that because of possible drug transfer into milk, women taking sirolimus should not breastfeed.[26]"

- **Micromedex** lactation rating is "infant risk cannot be ruled out. Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding."

- The **Reprotox** lactation summary includes a report of tacrolimus concentrations in mothers and their nursing infants, 1 of 15 mothers also reported receiving sirolimus during the course of pregnancy and lactation.[27] Tacrolimus blood concentrations in nursing infants declined over time and no adverse effects were noted. "We are not aware of additional studies on possible adverse effects of sirolimus exposure through lactation."

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[25] Bramham K, et al. Breastfeeding and tacrolimus: Serial monitoring in breastfed and bottle-fed infants. Clin J Am Soc Nephrol. 2013; 8:563-7.

[26] EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10.Pregnancy in renal transplant recipients. Nephrol Dial Transplant 2002; 17 (Suppl 4): 50-5.

[27] Bramham K, et al. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. Clin J Am Soc Nephrol. 2013 Apr;8(4):563-7. doi: 10.2215/CJN.06400612. PMID: 23349333; PubMed Central PMCID: PMC3613954.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal fertility studies have not been conducted with Hyftor gel. Fertility was decreased in both male and female rats following oral administration of sirolimus 2.0 and 5.0 mg/kg, respectively. In male rats, atrophy of testes, epididymides, prostate, seminiferous tubules and/or reduced sperm counts were observed. In female rats, decreased ovarian and uterine weights and decreased implantation were observed. Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at 0.1 mg/kg. For additional information, the reader is referred to the Nonclinical Review by Jill Merrill, PhD.

Clinical Experience

Clinical Trials

The applicant stated, "men and women of reproductive potential were included in all clinical trials with sirolimus gel (OSD-001-001, NPC-12G-1, NPC-12G-2 and NPC-12G-4/US) and no safety issues related to reproduction were noted."

Applicant's Review of the Published Literature

The applicant did not perform a published literature search related to sirolimus use and effects on fertility.

DPMH's Review of the Published Literature

This Reviewer performed a focused search in PubMed, Embase, and Reprotox[7] for relevant articles related to sirolimus use and effects on fertility. Search terms included: "topical sirolimus" OR "sirolimus" AND "fertility," "contraception," "oral contraceptives," OR "infertility."

No relevant publications were identified describing the use of topical sirolimus and effects on fertility. However, the following relevant publications were identified describing the use of oral sirolimus and potential effects on female and male fertility:

- The **Reprotox** section on reproduction cites the following clinical articles:
    - *Female fertility:* An open label trial of oral sirolimus given for autosomal dominant polycystic kidney disease treatment was associated with menstrual cycle disturbances consistent with irregular ovulation and the appearance of ovarian cysts in some women.[28]
    - *Male fertility:* There have been case reports and small studies in human transplant recipients suggesting that oral sirolimus therapy is associated with an increase in gonadotropin hormone concentrations and decreased testosterone production, sperm count, and fertility in men.[29,30,31,32,33,34,35,36,37]

[28] Braun M, et al. Low-dose oral sirolimus and the risk of menstrual-cycle disturbances and ovarian cysts: Analysis of the randomized controlled SUISSE ADPKD Trial. PLoS ONE 2012;7(10): e45868. doi:10.1371/journal.pone.0045868 https://www ncbi.nlm.nih.gov/pmc/articles/PMC3468602/

[29] Bererhi L, et al. Rapamycin-induced oligospermia. Transplantation 2003; 76: 885-886.

[30] Fritsche L, et al. Testosterone concentrations and sirolimus in male renal transplant patients. Am J Transplant 2004; 4: 130-131.

Reviewer's Comment
As noted above, DPMH met with the DDD Review Team (Clinical, Nonclinical, Clinical Pharmacology) to discuss whether or not the animal fertility studies with oral sirolimus were clinically relevant to Hyftor gel. Given several limitations in the available PK data for topical sirolimus which preclude the calculation of AUC and exposure multiples for comparison between humans and animals, the DDD Clinical Team concluded the W&P for Male Infertility will be retained in Hyftor gel as class labeling.

DISCUSSION/CONCLUSIONS

Pregnancy

Overall, the available data from 3 case reports of topical sirolimus gel, 0.2% use in pregnancy during the clinical development program are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Limited data from published reports of oral sirolimus use in pregnant women does not suggest an increased risk of adverse pregnancy outcomes but is also insufficient to draw conclusions regarding the safety of sirolimus use during pregnancy.

Animal reproduction studies have not been conducted with Hyftor gel. Subsection 8.1 of approved PLLR labeling for the listed drug, Rapamune, notes that based on animal studies and mechanism of action, oral sirolimus can cause fetal harm when administered to a pregnant woman. Per DPMH discussions with the DDD Review Team described above, the limited available pharmacokinetic data for topical sirolimus do not allow the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of Hyftor gel. Considering these data limitations preclude a clear determination of a safety margin with topical sirolimus administration, the DDD Clinical Team determined the W&P for Embryo-Fetal Toxicity from the listed drug, Rapamune, will be included in Hyftor gel labeling.

DPMH considered whether a postmarketing requirement for a single arm pregnancy safety study (SPSS) should be issued for Hyftor gel. However, considering angiofibroma associated with tuberous sclerosis is a rare disease and further that contraception is recommended during use of Hyftor gel due to the potential for embryofetal lethality observed in animal studies, it was determined that an SPSS would not likely be feasible.

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[31] Deutsch MA, et al. Sirolimus-associated infertility: Case report and literature review of possible mechanisms. Am J Transplant 2007; 7: 2414-2421.
[32] Skrzypek J, et al. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. Andrologia 2007; 39: 198-199.
[33] Zuber J, et al. Sirolimus may reduce fertility in male renal transplant recipients. Am J Transplant. 2008;8(7):1471-1479.
[34] Kaczmarek I, et al. Sirolimus impairs gonadal function in heart transplant recipients. Am J Transplant 2004; 4: 1084.
[35] Tondolo V, et al. Gonadal function and immunosuppressive therapy after renal transplantation. Transplant Proc 2005; 37: 1915.
[36] Lee S, Coco M, Greenstein SM, et al. The effect of sirolimus on sex hormone levels of male renal transplant recipients. Clin Transplant 2005; 19: 162.
[37] Huyghe E, et al: Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. Transpl Int. 2007 Apr;20(4):305-311.

Lactation

There are no available data on the presence of sirolimus in human milk, the effects on the breastfed infant, or the effects on milk production. Sirolimus was present in the milk of lactating rats. When a drug is present in animal milk, it is likely the drug will be present in human milk. However, the concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk. Approved PLLR labeling for the listed drug, Rapamune, and other mTOR inhibitors in class (such as everolimus and temsirolimus) states that there is a potential for serious adverse reactions in the breastfed infant. Given such, DPMH recommends including a breastfeeding is not recommended during treatment statement in Hyftor gel labeling.

DPMH considered whether a postmarketing lactation study should be required for Hyftor gel. Because breastfeeding is not recommended during use due to the potential for serious adverse reactions, it was determined that a lactation PMR will not be issued.

Fertility

There are no available data related to topical sirolimus administration and potential effects on male or female fertility. However, there are case reports and small retrospective studies in male transplant recipients that do suggest oral sirolimus administration may be associated with infertility. Further, fertility was decreased in both male and female rats following oral administration of sirolimus.

Subsection 8.3 of approved PLLR labeling for the listed drug, Rapamune, states "based on clinical findings and findings in animals, male and female fertility may be compromised." Per DPMH discussions with the DDD Review Team described above, the limited available pharmacokinetic data for topical sirolimus do not allow the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of Hyftor gel. Considering these data limitations which preclude a clear determination of a safety margin with topical sirolimus administration, the DDD Clinical Team determined the W&P for Male Infertility and subsection 8.3 statements from the listed drug, Rapamune, will be included in Hyftor gel labeling.

Considering the DDD Clinical Review Team determined the W&P for Embryo-Fetal Toxicity from the listed drug, Rapamune (oral sirolimus), will be included in Hyftor gel labeling, subsection 8.3 will also contain a "Contraception" heading. Rapamune labeling states the recommended duration of contraception is during treatment and 12 weeks after the final dose. It appears this recommendation is based on the recovery period for a nonclinical general toxicity study in rats.[38]

[38] Pharmacology/Toxicology PLLR Review of Rapamune (sirolimus) NDA 21083/S064 and NDA 2110/S083, by Andrew J. McDougal, PhD, DABT, DTOP, dated January 7, 2019. DARRTS Reference ID 4372170.

LABELING RECOMMENDATIONS

DPMH revised Highlights, subsections 5.7, 5.8, 8.1, 8.2, 8.3, and section 17 in Hyftor (sirolimus) gel, 0.2% labeling for compliance with the PLLR (see below). The recommendations below reflect input from the DDD Clinical, Nonclinical, and Clinical Pharmacology Review Teams. DPMH discussed the labeling recommendations below with DDD on June 17, 2020 and June 26, 2020. DPMH refers to the final NDA action for final labeling.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KRISTIE W BAISDEN
07/07/2020 01:01:55 PM

TAMARA N JOHNSON
07/10/2020 10:36:53 AM

LYNNE P YAO
07/14/2020 04:18:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: NDA 213478 HYFTOR™ (sirolimus) topical gel

FROM: Yasmin Choudhry, M.D.
Clinical Outcome Assessment (COA) Reviewer
Division of Clinical Outcome Assessment (DCOA)

Elektra Papadopoulos, M.D. MPH
Acting Director
DCOA

SUBJECT: DCOA review of the primary endpoint measure: "Composite Improvement in Angiofibroma scale (Size and redness)"

DRUG SPONSOR: Nobelpharma Co., Ltd.

COA TRACKING NUMBER: C2020155

Please check all that apply:

☒ Rare Disease/Orphan Designation
☒ Pediatric

EXECUTIVE SUMMARY

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by Division of Dermatology and Dentistry (DDD) on April 15, 2020 for NDA 213478 regarding topical HYFTOR™ (sirolimus) for the treatment of angiofibroma (AF) (adenoma sebaceum) associated with tuberous sclerosis. This COA consult is related to review of the content validity, inter-rater reliability, construct validity and the ability to detect change of the clinician-reported outcome (ClinRO) instrument (i.e., Composite Improvement in Angiofibroma) utilized to assess size and redness of facial AF lesions in the phase 3 study (Study NPC-12G-1) in conjunction with the photographic assessments.

Conclusion:

We do not consider the Composite Improvement in Angiofibroma scale to be an appropriate instrument to support regulatory decision making based on it's design (e.g., overlapping descriptors, multi-barreled items) and lack of sufficient supportive evidence of content validity (e.g., evidence of clinicians' understanding of the categories, descriptors, thresholds etc.) and inter- and intra-rater reliability (for details, see Review Findings below).
Additionally, given the scale assesses change in AF relative to BL and does not capture absolute severity, this was considered as a key limitation of the scale for use as a primary endpoint.

Therefore, clinical judgement should be used to decide whether and how to describe the improvement in the Composite Improvement in Angiofibroma scale in the product label. For detailed comments, see Review Findings below.

Future AF studies:

For future studies utilizing a ClinRO measure, it is important that 1) the design and content of the instrument is carefully planned based on the disease characteristics such that the clinicians have a clear understanding of the instrument content, and 2) the inter- and intra-rater reliability of the instrument is evaluated prior to its use in a confirmatory study. It is important to capture the patient's and/or caregiver perspectives. Most importantly, the Applicants should discuss their planned endpoints and COA selection or development (qualitative and quantitative) early in medical product development with the FDA. We recommend that sponsors review the 2009 Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm193282.pdf. We also recommend that sponsors utilize appropriate anchor measures in their clinical trials to enable the anchor-based methods to determine the clinically meaningful within-patient change in scores

BACKGROUND

Efficacy was supported by a single clinical trial (Study NPC-12G-1) conducted in Japan (no clinical trials were conducted in the US).

Study NPC-12G-1 was a randomized, double-blind, placebo-controlled study in adults and children (3 years and older) with AF (N=62). The study included a screening period, a 12-week double-blind period and a follow-up period. Per the study inclusion criteria, all subjects were to have 3 or more

papules of AF (≥ 2 mm in diameter with redness in each) on the face at screening.

The following ClinRO instruments were utilized in this study:

- Composite Improvement in Angiofibroma scale (Size and redness)
- Improvement in Size of Angiofibroma scale
- Improvement in Redness of Angiofibroma scale

For copies of these instruments, see Attachments 1, 2 and 3 of this review.

The primary endpoint for this study was: *The composite improvement in angiofibroma as assessed using photographs by the IRC (Independent Review Committee) members on photograph assessment at 12 weeks after the start of administration.*

The study assessments were completed at Weeks 4, 8, 12 and 4 weeks after end of drug administration by 3 IRC raters and Investigators. The assessments by the IRC raters were strictly based on the photographs while, the investigators conducted live photographic assessments (in comparison to baseline photographs) of patients at clinic sites. Of note, while baseline photographs were obtained for all subjects in the study, baseline scores of disease severity are not available.

Based on DDD's request, this review focused on the primary endpoint (i.e., assessments conducted by the IRC).

A summary of the procedures used to conduct the efficacy assessments by the IRC raters is as follows (for details, see the NDA submission)[1]:

- There were 3 IRC raters (all dermatologists) who reviewed the photographs of the AF lesions of each patient from all participating institutions to determine the improvement in AF independently from the Investigators[2] assessment.
- At the time of the assessments, the IRC raters had access to the photographs from previous time points (i.e., Weeks 4, 8 and 12) for comparison (overall improvement was compared to baseline photographs).
- It appears that the IRC raters first rated improvement in size, then redness and then the composite (size/redness) of the AF lesions in the photographs based on the 3 ClinRO instruments listed above.
- A total of three review sessions were conducted by the 3 IRC raters; 2 sessions each included 20 subjects' photographs and the third included 22 subjects' photos. If the independent ratings by 2 or more IRC raters were in agreement, that rating was to be used as the final score and the judgment was considered complete. After each IRC review session, a consensus discussion meeting was held to discuss cases on which there was complete disagreement among the independent ratings (i.e., all 3 IRC raters recorded a different score). The final IRC score for those cases was based on a consensus with concordance of 2 out of the 3 IRC raters; the details of the consensus process were not described raising questions about the validity of the process.

[1]See Materials Related to Independent Review Committee on Photograph Assessment, Case Review Committee, and Discussions with Medical Experts in Section 16.1.16 under Section 5.3.5.1 of the NDA submission.
[2]Investigators were specialists in the field of this disease or those with equivalent experience and knowledge.

REVIEW FINDINGS

Content Validity: Composite Improvement in Angiofibroma scale (Size and redness)

Importantly, content validity is the degree to which a COA measures the concept of interest; other measurement properties i.e., construct validity, reliability and ability to detect change are not meaningful without evidence of content validity. We have the following concerns regarding this instrument:

1. A key limitation of the scale for use as a primary endpoint is that it assesses change in AF relative to BL and does not capture absolute severity. The scales used to assess size and redness, respectively, were also ratings of change. Therefore, we do not have information on quantifying angiofibroma severity.

2. The NDA submission does not include any qualitative evidence in support of this instrument. It is unclear how the scales composing the instrument were developed and whether they were cognitively tested in clinicians for their understanding of the different categories, descriptors, thresholds etc.

3. The categories of change appear to have over-lapping descriptors (e.g., shrinkage, flattening, or disappearance). It is important that response categories should be distinct (i.e., non-overlapping) and should represent a clinically meaningful gradation of disease.

4. The descriptors for all categories are either double- or triple-barreled (e.g., Category Markedly improved: *Shrinkage, flattening, or disappearance of tumors is observed overall*. Use of multi-barreled items is generally discouraged as they do not allow assessment and reporting of each component within the multi-barreled item and could lead to inconsistent reporting by respondents.

5. Each category includes two concepts (i.e., size and redness of AF lesions). Assessing improvement in two different concepts (such as size and redness) under one item can be confusing for the respondents and may generate inconsistent reporting. It is possible that improvement could be observed in one and not the other concept. Interpreting results from such items can be challenging. However, in this study, the IRC raters were instructed to first assess AF size, then color followed by the composite assessment.

Inter-rater reliability

Based on the evidence submitted, the reliability (inter-rater reliability) of the Composite Improvement in Angiofibroma instrument is questionable because of the following reasons:

- As discussed above, Study NPC-12G-1 utilized an instrument that was not content valid and was not well-designed.
- Additionally, the methodology of assessments used by the IRC raters does not give us confidence in the results of their reviews. For example,
  - The raters were not blinded to the assessments from previous time points.
  - Assessments were not conducted on original photographs.

Ideally, reliability of the instrument should be evaluated prior to its use in a confirmatory study. Of note, the intra-rater reliability of the instrument was not evaluated in this study.

IRC procedures of assessments

We have concerns regarding the procedures utilized by the IRC raters to complete the assessments (i.e., independent review by the 3 IRC raters followed by consensus discussion meetings resulting in modifying the rating):

- It is possible that some raters may have been influenced by the other raters or may or may have felt pressured in offering their true rating.
- While the IRC raters were blinded to the treatment, they were not blinded to the assessments from other time points (before and after treatment photographs were displayed on their monitors for comparison). The raters may have been influenced (in either direction) by a previous time point rating.
- The final score could be modified based on the consensus discussions. A rationale for conducting the consensus discussions was not included in the submission. Additionally, changing the scores of several assessment during the trial raises concern that the instrument may be problematic.

Instructions for conducting assessments

The Applicant's instructions on conducting the assessments (for the IRC raters) is shown in the snapshot below (taken from Section 3 of the instructions submitted under Section 16.1.1: *Protocol and Protocol Amendments*, NDA submission).

3. OVERALL IMPROVEMENT IN ANGIOFIBROMAS

Improvement in angiofibromas will be assessed by first performing assessments described in Section 3.1. "Improvement in Size of Angiofibromas" and Section 3.2. "Improvement in Redness of Angiofibromas" and then assessing "composite improvement in angiofibromas" as an overall assessment is performed taking into consideration the results of the above assessments and the clinical significance thereof in the subject.

While we do not agree with the overall methodology (as discussed above) of assessments used in this trial, on face, the instructions (including instructions on how to assess size and redness of the AF lesions) appeared reasonable.

Other measurement properties

We are unable to comment on the other measurement properties (i.e., construct validity and ability to detect change etc.) as the submission did not include any related evidence. It appears that a psychometric study was not conducted.

Attachments

Attachment 1: Composite Improvement in Angiofibroma scale

Attachment 2: Improvement in Size of Angiofibroma scale
Attachment 3: Improvement in color of Angiofibroma
Attachment 4: Results of Independent Assessment by IRC Raters
Attachment 5: NPC-12G-1 First Independent Review Committee on Photograph Assessment: Results of Discussion

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Memo To File

Date	2 June 2020
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Strother Dixon, Senior RPM Patricia Brown, MD, Medical Reviewer Kevin Clark, MD, Medical Reviewer Gordana Diglisic, MD, Medical Team Leader Kendall Marcus, MD, Division Director, Division of Dermatology and Dentistry (DDD)
NDA #	213478
Applicant	Nobelpharma Co., Ltd.
Drug	NPC-12G gel, aqueous gel formulation containing 2 mg sirolimus (0.2% w/w)
NME	No
Proposed Indication	For the treatment of facial angiofibromas associated with tuberous sclerosis complex
Consultation Request Date	19 March 2020
Summary Goal Date	17 June 2020
Priority/Standard Review	Priority
Action Goal Date	4 August 2020
PDUFA Date	18 August 2020

A consult to conduct inspections was received from the Division of Dermatology and Dentistry (DDD) on 19 March 2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections: Drs. Ono (Site 4, Tokyo, Japan) and Kaneda (Site6, Osaka, Japan).

At the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of NDA 213478 was reevaluated. Following discussions between OSI and DDD, a decision was made that assessment of the application could proceed without GCP inspections. OSI will therefore be unable to determine if Protocol NPC-12G-1 was conducted adequately and whether the study data are reliable in support of the proposed indication at this time.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
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Good Clinical Practice Assessment Branch
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OSI/DCCE/GCPAB/Reviewer/Cheryl Grandinetti
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 21, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213478
Product Name, Dosage Form, and Strength:	Hyftor (sirolimus) gel, 0.2%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Nobelpharma Co., Ltd.
FDA Received Date:	February 18, 2020 and May 11, 2020
OSE RCM #:	2020-327
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the approval process for Hyftor (sirolimus) gel, (b) (4), the Division of Dermatology and Dentistry (DDD) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), container label, and carton labeling and found the MG acceptable from a medication error perspective. However, we note the PI can be improved to provide clarity on the package configuration and to facilitate product identification. We also note the container label and carton labeling can be improved to prominence of important information (e.g. established name, (b) (4) storage conditions), to prevent wrong dose errors, and to facilitate product identification.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved to increase the prominence of important information, prevent wrong dose errors, and to facilitate product identification. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

a. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-XX). Replace this NDC placeholder with the actual NDC on both the container label and carton labeling when it is determined.

b. We note the net quantity is not included (i.e. 10 g). Consider adding this information next to "aluminum tube".

4.2 RECOMMENDATIONS FOR NOBELPHARMA CO., LTD.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. The strength statement, 0.2 %, appears far away from the product name and dosage form. To facilitate product identification, we recommend relocating the strength statement to appear closer to product name and dosage form statement.

3. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-XX). Replace this NDC placeholder with the actual NDC on both the container label and carton labeling when it is determined.

4. Add the statement [redacted] (b) (4) or similar statement prominently displayed on the Principal Display Panel (PDP) in accordance with 21 CFR 208.24(d).

5. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read [redacted] (b) (4) If space is limited, the statement may read "Recommended Dosage and Administration: See prescribing information."

6. Revise and bold the statement "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

7. We recommend a hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling

1. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 2 mg/g instead of 2mg/g).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Hyftor received on May 11, 2020 from Nobelpharma Co., Ltd., and the listed drug (LD).

Table 2. Relevant Product Information for Hyftor and the Listed Drug		
Product Name	Hyftor	Rapamune (NDA 021110)[a]
Initial Approval Date	N/A	August 25, 2000
Active Ingredient	sirolimus	sirolimus
Indication	treatment of angiofibroma associated with tuberous sclerosis in adults and children (b) (4) of age and older.	prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants.
Route of Administration	topical	oral
Dosage Form	gel	tablet
Strength	0.2%	0.5 mg, 1 mg, 2 mg
Dose and Frequency	Apply (b) (4) to the affected skin with angiofibroma twice daily. (b) (4)	<u>In renal transplant patients</u> • Take once daily by mouth, consistently with or without food. Take the initial dose as soon as possible after transplantation and 4 hours after CsA. Adjust the Rapamune maintenance dose to achieve sirolimus trough concentrations within the target-range. <u>Patients at low-to moderate-immunologic risk</u> • Rapamune and Cyclosporine Combination Therapy: A loading dose of Rapamune equivalent to 3 times the maintenance dose should be given, i.e. a daily maintenance dose of 2 mg should be preceded with a loading dose of 6 mg. Therapeutic drug monitoring should be used to maintain

[a] Rapamune (sirolimus) [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 May 06. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021083s067,021110s085lbl.pdf.

		sirolimus drug concentrations within the target-range • Rapamune Following Cyclosporine Withdrawal: 2-4 months post-transplantation, withdraw CsA over 4-8 weeks. <u>Patients at high-immunologic risk</u> • Rapamune and Cyclosporine Combination Therapy (for the first 12 months post-transplantation): One loading dose of up to 15 mg on day 1, followed by daily maintenance doses of 5 mg. A trough level should be obtained between days 5 and 7, and the daily dose of Rapamune should thereafter be adjusted. The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses and the dose should subsequently be adjusted to achieve target whole blood trough concentrations. <u>In lymphangioleiomyomatosis patients</u> • Take once daily by mouth, consistently with or without food. The initial Rapamune dose should be 2 mg/day. Adjust the Rapamune dose to achieve sirolimus trough concentrations between 5-15 ng/mL.
How Supplied	10 g tube	0.5 mg and 1 mg: Bottles of 100 tablets and Redipak cartons of 10 blister cards of 10 tablets each 2 mg: Bottles of 100 tablets
Storage	Store at refrigerated at 2-8°C (36-46°F).	stored at 20°C to 25°C [USP Controlled Room Temperature] (68°F to 77°F).
Container Closure	Aluminum tube	Bottle, Carton

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Hyftor labels and labeling submitted by Nobelpharma Co., Ltd..

- Container label received on February 18, 2020
- Carton labeling received on February 18, 2020
- Prescribing Information and Medication Guide (Image not shown) received on May 11, 2020, available from \\cdsesub1\evsprod\nda213478\0011\m1\us\114-labeling\draft\labeling\hyftor-draft-labeling-text-word-version.docx

G.2 Label and Labeling Images

Container Label

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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