

Memorandum

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

Date: June 28, 2020

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

To: To Executive Summary, IQA for Assessment # 1 of NDA 213422

Subject: Final Recommendation of "Approval"

In original IQA review dated June 19, 2020, this NDA was not recommended for approval in the form it was presented due to unresolved labeling/labels issues identified by the Drug Product Reviewer, Dr. Hong Cai as per 21 CFR 314.125(b)(6). The applicant submitted revised container and carton labels on June 22, 2020 and revised PI labeling on June 25, 2020. The revised labeling and labels have been reviewed by Dr. Cai on June 25, 2020 and found to be adequate to support the approval of this application from the CMC labeling and labels perspective (see the Attachment).

Therefore, from the OPQ perspective, this NDA is now recommended for **approval**.

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

Attachment

Memorandum

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

Date: June 25, 2020

From: Hong Cai, Ph.D.
Drug Product Reviewer
Office of New Drug Products
Branch IV/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Office of New Drug Products
Branch IV/DNDP II

To: Drug Product/Labeling Review #1 of NDA 213422
for WYNZORA® (calcipotriene and betamethasone dipropionate)
cream

Subject: Final Recommendation

The Labeling Review #1 dated April 30, 2020 recommended that NDA 213422 was not ready for approval in the form it was presented due to the prescribing information (PI) labeling as well as container and carton labels deficiencies from the CMC perspective. The applicant, MC2 Therapeutics has submitted the revised carton labeling and container labels on June 22, 2020 (SN0029) and PI labeling on June 25, 2020 (SN0030), respectively. The revised labeling and labels have satisfactorily resolved the deficiencies related to CMC sections (Carton and Container Labeling/Label, Highlights of PI and Section #3, #11 and #16 of Full PI) that were delineated in Labeling Review #1 (see Appendix I and Appendix II).

Note that based on the recommendation from the clinical and labeling teams, “cream” is used as part of the drug product name and is capitalized as “Cream” throughout PI as “WYNZORA Cream” (See Appendix-III the email communication with the clinical reviewer Dr. Kevin Clark on June 16, 2020).

Recommendation:

This application is now recommended for **approval** from the CMC labeling/labels perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch IV, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch IV, Division II, ONDP



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Rhee

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Hamid
Shafiei

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substances, calcipotriene and betamethasone dipropionate, and the fixed-dose combination drug product, WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.0005%/0.064% intended for topical administration.
- Labels/labeling issues have **not** been **satisfactorily** addressed.
- The Office of Process and Facility has made an overall “**Acceptable**” recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is deemed **not ready** for **APPROVAL** in its present form per 21 CFR 314.125(b)(6), until the deficiency noted in the **List of Deficiencies** is satisfactorily resolved.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

MC2 Therapeutics Ltd. has submitted this (505)(b)(2) new drug application for a fixed-dose combination drug product, WYNZORA[®] (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%. This drug product is intended for topical administration for the treatment of plaque psoriasis in patient 18 years of age or older. It is to be topically applied once daily to affected skin area for up to 8 weeks.

Taclonex Ointment (NDA 21852) and Taclonex Topical Suspension (NDA 22185) are used as the listed drugs. Both Taclonex[®] Ointment and Taclonex[®] topical suspension are fixed-dose combination of the two active ingredients in WYNZORA[®] and at the same strengths.

The active ingredient, calcipotriene is a synthetic analogue of vitamin D with immunomodulatory effects comparable to natural vitamin D. The active ingredient, betamethasone dipropionate is a synthetic fluorinated corticosteroid and its potency is dependent on the formulation. Betamethasone dipropionate has metabolic, pharmacological, and

toxicological effects typical for corticosteroids with anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties. Betamethasone dipropionate has been classified as a potent steroid in Taclonex[®] Ointment.

WNYZORA[®] cream for commercial use is packaged as 60g in aluminum tube with (b) (4) screw cap.

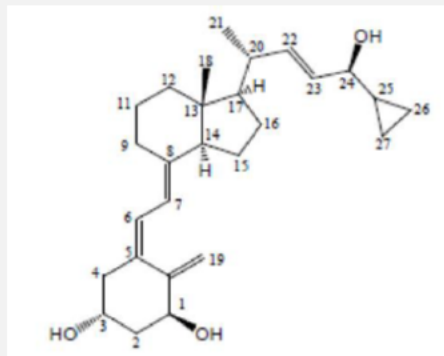
Proposed Indication(s) including Intended Patient Population	Treatment of plaque psoriasis in patients 18 years of age or older.
Duration of Treatment	8 weeks.
Maximum Daily Dose	It is to be topically applied to affected skin area once daily
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug product, WNYZORA Cream is fixed-dose combination containing two drug substances, anhydrous calcipotriene and betamethasone dipropionate.

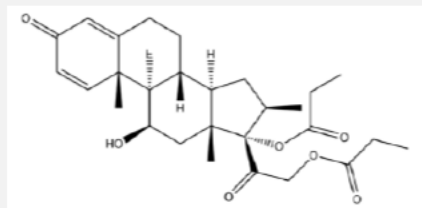
- 1) Calcipotriene is a synthetic analogue of vitamin D3 and has immunomodulatory effects comparable to natural vitamin D. Calcipotriene is a white to almost white powder. It is insoluble in water, freely soluble in ethanol, and slightly soluble in methylene chloride. Calcipotriene has the chemical name of (5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochole-5,7,10(19),22-tetraene-1 α ,3 β ,24-triol, molecular weight of 412.6, molecular formula of C₂₇H₄₀O₃, and the molecular structure below:



Anhydrous calcipotriene for this application is manufactured in compliance to current good manufacturing practices (cGMP) requirement by (b) (4). (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4). It is tested and released against a drug substance specification that assures the identity, strength, purity, and quality of calcipotriene at release and throughout its assigned retest period of (b) (4) months when stored at (b) (4) and/or retest period of (b) (4) months when stored at (b) (4). Anhydrous calcipotriene manufactured by (b) (4) complies to the requirements in the USP monograph for this drug substance.

Detailed information regarding the manufacture of anhydrous calcipotriene by (b) (4) is provided in DMF (b) (4). This DMF was reviewed by the Drug Substance Reviewer, Dr. Jeffry Medwid on October 5, 2019 and was found to be adequate.

- 2) Betamethasone dipropionate is a synthetic corticosteroid with anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties. Betamethasone dipropionate is a white to almost white crystalline powder with a melting point of 170°C -179°C with decomposition. It is insoluble in water, freely soluble in acetone and methylene chloride, and sparingly soluble in alcohol. Betamethasone dipropionate has the chemical name of 9 α -fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione-17,21-dipropionate, molecular weight of 504.6, molecular formula of C₂₈H₃₇FO₇, and molecular structure below:



Betamethasone dipropionate for this application is manufactured in compliance to cGMP requirements by (b) (4). It is packaged in (b) (4) and is tested against a drug substance specification that assures the identity, strength, purity, and quality of betamethasone dipropionate at release and throughout of its proposed retest period of (b) (4) when stored at

(b) (4) Betamethasone dipropionate manufactured by (b) (4) complies to the requirement in the USP monograph for this drug substance.

Detailed information regarding the manufacture of betamethasone dipropionate by (b) (4) is provided in DMF (b) (4). This DMF was reviewed by Drug Substance Reviewer, Dr. Wei Song on January 4, 2018 and was found to be adequate.

In summary, relying on Dr. Song review of DMF 17047, the Drug Substance Reviewer for this application, Dr. Jeffery Medwid has found the information submitted in DMF (b) (4) and DMF (b) (4) as well as the information submitted in the drug substance module of this application adequate to support the approval of this application from the drug substance perspective. Dr. Medwid's review is provided in the Drug Substance Chapter of the IQA.

Drug Product: Adequate

WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% has been developed for the treatment of plaque psoriasis in patients 18 years of age or older. Taclonex Ointment and Taclonex Topical Suspension at the same strength are used as the listed drugs for this application.

Each gram of WYNZORA cream contains 50 mcg of calcipotriene and 0.644mg of betamethasone dipropionate as the active ingredients and isopropyl myristate, mineral oil, medium-chain triglyceride, isopropyl alcohol, polyoxyl lauryl ether, poloxamer (407), polyoxyl 40 hydrogenated castor oil, carbomer interpolymer type A, butylated hydroxyanisole (BHA), trolamine, dibasic sodium phosphate, monobasic sodium phosphate, DL-A-tocopherol, and purified water as inactive ingredients. Inactive ingredients used in the composition of the drug product are all compendial material with exception of carbomer interpolymer type A. This excipient had not been previously approved in any topical drug product. The use of carbomer interpolymer type A in the composition of the drug product was evaluated by the Pharm/Tox Reviewer, Dr. Carmen Brooks. Dr. Brooks has concluded that there are no safety concerns associated with the use of this excipient in the composition of the drug product. The amounts of the compendial excipients used in the composition of the drug product are at or below the maximum levels approved in the FDA inactive ingredients database (IID) for topical drug products.

WYNZORA Cream is manufactured by (b) (4) for MC2 Therapeutics Ltd. in compliance with the cGMP requirement and is packaged as 60g in aluminum tubes. The drug product is tested and released against a specification that assures the identity, strength, purity,

and quality of the drug product at release and throughout its proposed shelf-life of 24 months. The applicant has provided sufficient stability data that supports the expiration dating period of 24 months.

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

Labeling: Inadequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Hong Cai. Dr. Cai has noted PI labeling as well as container and carton labels deficiencies (see the List of Deficiencies) and recommended that this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiency is satisfactorily resolved. Dr. Cai's labeling/labels review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

The manufacturing process for WYNZORA Cream is comprised of

(b) (4)

(b) (4) Therefore, the overall manufacturing process for WYNZORA Cream is considered adequate.

As the result of inspection of the drug product manufacturing facility, (b) (4) (b) (4) three 483 observations were issued. Although the response to the 483 observations are still pending due to the agreed date of response of (b) (4), based on the applicant's response to subsequent drug product IR letters, and the review of the applicant's response, the risk to the drug product associated with these observations

were deemed low, and were subsequently reclassified as voluntary actions. Therefore, all facilities involved in the manufacturing of WYNZORA Cream have been determined as adequate.

The manufacturing section (process and facilities) of this application has been reviewed by the OPMA Reviewer, Dr. Youmin Wang. Dr. Wang has recommended the approval of this application from the manufacturing perspective. Dr. Wang's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

From the Biopharm stand point, the formulation intended for commercial drug product is the same formulation used in Phase 3 clinical studies and therefore, there is no need for any bridging study.

The applicant did not include an in-vitro release test (IVRT) method as an additional measure for drug product quality. A general advice letter was sent to applicant on November 13, 2019 requesting for the development of IVRT method as quality control measure for the cream drug product. The applicant responded to the Biopharm advise letter on November 29, 2019 stating that IVRT is not applicable for routine release and stability testing of semi-solid drug product according to SUPAC-SS. (b) (4)

The applicant's response was accepted.

Biopharm section of this application has been reviewed by the Biopharm Reviewer, Dr. Min Li. Dr. Li has found the information provided in the Biopharm section of this application adequate and has recommended the approval of this application from the Biopharm perspective. Dr. Li's brief review is provided in the Biopharm Chapter of the IQA.

Microbiology (if applicable): Adequate

WYNZORA (calcipotriene/betamethasone dipropionate) Cream is a non-sterile drug product. The applicant has provided methods for the control of bioburden according to USP <60>, USP <61>, and USP <62>. The applicant has provided information regarding antimicrobial effectiveness testing (b) (4)

. The applicant has also provided supporting data from testing of the registration batches of drug product at release and during stability for bioburden to show that bioburden is well-controlled during drug product shelf-life storage. Additionally, the applicant has included testing and acceptance for bioburden according to USP <60>, USP <61>, and USP <62> in the drug product specification.

The microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Alifiya Ghadiali. Dr. Ghadiali has concluded that the information provided in the microbiology section of this application adequate and has recommended approval of this application from the microbiology perspective. Dr. Ghadiali's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Immediate container integrity during in- use stability (b) (4)	Drug product degradation and bioburden	M	(b) (4)	L Since this is a non- sterile drug product for topical use	(b) (4)

D. List of Deficiencies for Complete Response

Labeling Deficiencies

- A. Prescribing information**
- The Highlights Section:**
- 1) Revise "Cream" to lower case "cream" in the product title.
 - 2) Revise "Dosage Forms and Strengths" to "Cream:
0.005%/0.064%"

Full Prescribing Information Section:

1. Dosage Forms and Strengths (Section 3):

- 1) Revise “(b) (4)” to “0.644 mg of betamethasone dipropionate” per drug product composition table in NDA if confirmed by the applicant.
- 2) Revise “Each gram of WYNZORA™ Cream” to “Each gram of Tradename cream”. “Cream” should be presented as lower case “cream”.

2. Description (Section #11):

- 1) Add the established name of the drug product “calcipotriene and betamethasone dipropionate cream”.
- 2) Suggest revising “calcipotriene anhydrate” to “anhydrous calcipotriene”. This applies to the entire PI document.
- 3) Remove “(b) (4)” from the statement “Chemically, calcipotriene is (5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22 tetraene-1 α ,3 β ,24-triol,…”
- 4) The following important chemical or physical property information of the active ingredients, anhydrous calcipotriene and betamethasone dipropionate should be added per information provided in NDA:

Calcipotriene is a white or almost white powder. It is insoluble in water, freely soluble in ethanol and slightly soluble in methylene chloride.

Betamethasone dipropionate is a white to almost white crystalline powder. It is practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

Recommend listing the inactive ingredients as per USP/NF names instead of the brand names.

- 5) Remove the following statement which sounds promotional: ‘(b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

3. How Supplied/Storage and Handling (Section 16):

- 1) Add the drug product strength presentation.
- 2) Add the actual NDC number of the product.
- 3) Add "Protect from light and excessive heat".
- 4) Add "Unused product should be discarded six months after the tube has been opened."

B. Container Labels and Carton Labeling:

- 1) The product title and strength should be presented as following:

Tradename

(calcipotriene and betamethasone dipropionate) cream,
0.05%/0.064%

- 2) The size of the established name must be at least 50% of the tradename.
- 3) For clarity and consistency, revise the active and inactive ingredient list statement to be consistent with that in Description (Section 11) of PI. Additionally, add the equivalency statement of betamethasone dipropionate to betamethasone. Confirm the amount of betamethasone dipropionate per gram of cream is 0.644 mg (b) (4) as indicated in the drug product composition table in NDA and revise your statement accordingly.
- 4) Revise the statement of the storage condition to ensure that it is consistent with the storage condition listed in "How Supplied/Storage and Handling" (Section #16) of PI. And also include the following statements:

Protect from light and excessive heat.
Unused product should be discarded six months after the tube has been opened.
- 5) Add the statement "Rx only"
- 6) Add the lot number and expiry date.
- 7) Revise the statement "(b) (4)" to "See package insert for dosage information".
- 8) Remove the following statement on carton labeling which are deemed promotional:

(b) (4)

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



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Shafiei

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Review of the Prescribing Information is based on the submission on 03/20/2020 (SN0012). Only the sections related to the drug product quality: product title and dosage forms and strengths in the highlight section and section #3, #11 and #16 of Full Prescribing Information of PI are assessed in this review.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION



Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	WYNZORA™	Satisfactory
Established name(s)	(calcipotriene and betamethasone dipropionate) Cream	Not Satisfactory Revise "Cream" to lower case "cream"
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Cream, 0.005%/0.064% (b) (4)	Not Satisfactory Detailed description is recommended to move to Section #3 of full prescribing information.

	(b) (4)	Revise to: Cream, 0.005%/0.064% (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	Not Applicable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not Applicable	Not Applicable

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2 DOSAGE AND ADMINISTRATION



Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Not Applicable	Not Applicable The formulation is cream for topical use only and there is no further reconstitution needed prior to administration.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS



Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Cream	Satisfactory
Strength(s) in metric system	0.005%/0.064%	Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	WYNZORA™ Cream is a white cream	Satisfactory
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	Not Applicable
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not Applicable	Not Applicable

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	WYNZORA™ Cream	Not Satisfactory Add the established name and present as the following: Tradename (calcipotriene and betamethasone dipropionate) cream
Dosage form(s) and route(s) of administration	Cream It is intended for topical use only.	Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each gram of WYNZORA™ Cream contains 50 mcg of calcipotriene anhydrate and (b) (4) mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)	Satisfactory
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Not Satisfactory Recommend list the inactive ingredients as per USP/NF names instead of the brand names.

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not Applicable	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Not Applicable
Statement of being sterile (if applicable)	Not Applicable	Not Applicable
Pharmacological/ therapeutic class	Calcipotriene anhydrate is a synthetic vitamin D3 analog. Betamethasone dipropionate is a synthetic corticosteroid.	Satisfactory

Chemical name, structural formula, molecular weight	(b) (4)	Not Satisfactory To keep the presentation consistency with USAN dictionary, minor edition was made with the chemical name of betamethasone dipropionate shown as the following: Pregna-1,4-diene-3,20-dione, -9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxypropoxy)-, (11β, 16β)
If radioactive, statement of important nuclear characteristics.	Not Applicable	Not Applicable

Other important chemical or physical properties (such as pKa or pH)	Not Specifically Mentioned	Not Satisfactory Provide the important chemical or physical properties for anhydrous calcipotriene and betamethasone dipropionate.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not Applicable	Not Applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	(b) (4)	This Statement sounds promotional and is recommended for removal.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING



Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	WYNZORA™ Cream	Not Satisfactory Revise "Cream" to "cream".
Strength(s) in metric system	Not provided	Not Satisfactory Add the strength: 005%/0.064%, Each gram of Tradename cream contains 50 mcg of calcipotriene anhydrate and 0.644 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).
Available units (e.g., bottles of 100 tablets)	It is available as 60 g tubes (NDC 73499-001-01).	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	WYNZORA™ Cream is a white cream.	Satisfactory
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	Not Applicable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not Applicable	Not Applicable

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Do not freeze. Protect from light and excessive heat.	Not Satisfactory Add the following statement: <i>Unused product should be discarded six months after the tube has been opened.</i>
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	Not Applicable	Not Applicable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store between 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). [See USP controlled room temperature.]	Satisfactory
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	Not Applicable	Not Applicable
Include information about child-resistant packaging	Not Applicable	Not Applicable

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by MC2 Therapeutics, Inc., Dover, DE 19901, US (b) (4)	Not Satisfactory Delete the following statement which appears promotional: (b) (4)

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Wynzora™ Calcipotriene 0.005% and betamethasone dipropionate 0.064% Cream	Not Satisfactory • Revise to Tradename (calcipotriene and betamethasone dipropionate) cream, 0.005%/0.064% • The size of the established name must be at least 50% of the tradename.
Dosage strength	Calcipotriene 0.005% and betamethasone dipropionate 0.064% Cream	Not Satisfactory See the comments above for the presentation format
Route of administration	For Topical Use Only	Satisfactory
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not provided	Not Satisfactory Recommend including the equivalency statement of betamethasone for betamethasone dipropionate, because there are previously approved drug products based on the active moiety, betamethasone.

Inactive ingredient statement (Quantitative ingredient information for injectables)	(b) (4)	Not Satisfactory Recommend listing the inactive ingredients as per USP/NF names instead of the brand names.
Net contents (e.g. tablet count)	Net Wt. 60 g	Satisfactory
“Rx only” displayed on the principal display	Not provided	Not Satisfactory Include “Rx only” on the principal display
NDC number	NDAXXXXXX XXX XX	Not Satisfactory Include the actual NDA number
Lot number and expiration date (21 CFR 201.17)	Not Provide	Not Satisfactory Provide the lot number and expiration date
“See package insert for dosage information”	See Insert for complete information	Not Satisfactory Revise the statement “See Insert for complete information” to “See package insert for dosage information”
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage: Store between 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). [See USP controlled room temperature]. Do not freeze.	Not Satisfactory Add the following statement to be consistent with the storage conditions stated in Section 16 of PI: “Protect from light and excessive heat. Unused product should be discarded six months after the tube has been opened.”

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not Applicable	Not Applicable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not Applicable	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Not Applicable
Bar code	Provided on Carton Labeling	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	MC2 therapeutics Distributed by MC2 Therapeutics, Inc. Dover, DE 19901, USA	Satisfactory Remove the following statement which appears promotional:  (b) (4)
Medication Guide (if applicable)		
No text on Ferrule and Cap Overseal	Not Applicable	Not Applicable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not Applicable	Not Applicable
And others, if space is available		

Assessment of Carton and Container Labeling: *Inadequate*

This review is based on the carton and container labels submitted on March 20, 2020 (SN0012). The identified deficiencies are delineated **at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."**

ITEMS FOR ADDITIONAL ASSESSMENT

LIST OF DEFICIECIES:

A. Prescribing information

The Highlights Section:

- 1) Revise “Cream” to lower case “cream” in the product title.
- 2) Revise “Dosage Forms and Strengths” to “Cream: 0.005%/0.064%”

Full Prescribing Information Section:

1. Dosage Forms and Strengths (Section 3):

- 1) Revise “(b) (4) mg of betamethasone dipropionate” to “0.644 mg of betamethasone dipropionate” per drug product composition table in NDA if confirmed by the applicant.
- 2) Revise “Each gram of WYNZORA™ Cream” to “Each gram of Tradename cream”. “Cream” should be presented as lower case “cream”.

2. Description (Section #11):

- 1) Add the established name of the drug product “calcipotriene and betamethasone dipropionate cream”.
- 2) Suggest revising “calcipotriene anhydrate” to “anhydrous calcipotriene”. This applies to the entire PI document.
- 3) Remove “(b) (4)” from the statement “Chemically, calcipotriene is (5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22 tetraene-1 α ,3 β ,24-triol,…”
- 4) The following important chemical or physical property information of the active ingredients, anhydrous calcipotriene and betamethasone dipropionate should be added per information provided in NDA:

Calcipotriene is a white or almost white powder. It is insoluble in water, freely soluble in ethanol and slightly soluble in methylene chloride.

Betamethasone dipropionate is a white to almost white crystalline powder. It is practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

- 5) Recommend listing the inactive ingredients as per USP/NF names instead of the brand names.
- 6) Remove the following statement which sounds promotional:



3. How Supplied/Storage And Handling (Section 16):

- 1) Add the drug product strength presentation.
- 2) Add the actual NDC number of the product.
- 3) Add "Protect from light and excessive heat".
- 4) Add "Unused product should be discarded six months after the tube has been opened."

B. Container Labels and Carton Labeling:

- 1) The product title and strength should be presented as following:

Tradename
(calcipotriene and betamethasone dipropionate) cream, 005%/0.064%

- 2) The size of the established name must be at least 50% of the tradename.
- 3) For clarity and consistency, revise the active and inactive ingredient list statement to be consistent with that in Description (Section 11) of PI. Additionally, add the equivalency statement of betamethasone dipropionate to betamethasone. Confirm the amount of betamethasone dipropionate per gram of cream is 0.644 mg instead of (b) (4) mg as indicated in the drug product composition table in NDA and revise your statement accordingly.
- 4) Revise the statement of the storage condition to ensure that it is consistent with the storage condition listed in "How Supplied/Storage And Handling" (Section #16) of PI. And also include the following statements:

Protect from light and excessive heat.

Unused product should be discarded six months after the tube has been opened.

- 5) Add the statement "Rx only"
- 6) Add the lot number and expiry date.
- 7) Revise the statement [REDACTED] (b) (4) to "See package insert for dosage information".
- 8) Remove the following statement on carton labeling which are deemed promotional:

[REDACTED] (b) (4)

Overall Assessment and Recommendation:

There are still deficiencies not fully resolved as of this review in the submitted PI and Carton and Container labeling and labels, which are delineated in the above "List of Deficiencies".

It is also noted that "Tradenname" is used as the recommended proprietary name until one is approved by FDA.

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

Primary Labeling Assessor Name and Date:

Hong Cai, Ph.D.

Drug product Reviewer

Branch IV/DNDP II/ONDP/OPQ

Date of Review: April 21, 2020

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

I agree with Dr. Cai's assessment on the labeling and labels and concur with her recommendation that this application is not deemed ready for approval in its

present form per 21 CFR314.125(b)(6) until the issues delineated in the List of Deficiencies are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.

Chief, Branch IV

DNDPII/ONDP/OPQ

4/24/2020

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Rhee

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BIOPHARMACEUTICS

NDA: 213422

Submission Type: 505(b)(2)

Drug Product Name/Strength: MC2-01 cream (calcipotriene/betamethasone dipropionate cream, 0.005%/0.064%)

Route of Administration: Topical

Applicant Name: MC2 Therapeutics Ltd (part of MC2 Therapeutics)

Submission:

MC2 Therapeutics Ltd. submitted this 505(b)(2) application on Sep 20, 2020 for Calcipotriene (CAL)/Betamethasone dipropionate (BDP) Cream, 0.005%/0.064% intended for the treatment of plaque psoriasis by topical administration. This proposed drug product is a fixed dose combination of calcipotriene, an analogue of vitamin D, and betamethasone, a fluorinated synthetic corticosteroid. The Listed Drug (LD) products are Taclonex® (CAL/BDP, 0.005%/0.064%) Ointment (LEO Pharma, NDA#021852) and Taclonex® (CAL/BDP 0.005%/0.064%) Topical Suspension (LEO Pharma, NDA#022185). Clinical studies including PK/PD, efficacy and safety studies were conducted to support the approval of proposed drug product.

Review Summary: ADEQUATE

The proposed cream formulation was developed (b) (4)

The proposed commercial formulation is same as that for phase 3 clinical studies; therefore, there is no need for formulation bridging.

There is no in vitro release test (IVRT) proposed for quality control of the drug product. Biopharmaceutics general advice comments which recommend IVRT method development and using IVRT for quality control of the drug product were sent to the Applicant on Nov 13, 2019 (see Appendix). In response received on Nov 29, 2019, the Applicant stated that IVRT is not applicable for routine release and stability testing of semi-solid drug product based on SUPAC-SS (Scale-Up and Post-Approval Changes Non-Sterile Semisolid) dated May 1997. (b) (4)

The response is acceptable.

This NDA213422 is recommended for **APPROVAL** from a biopharmaceutics perspective.

The following general advice is recommended to be conveyed to the Applicant:

For future post-approval changes, the Agency recommends that you develop an in vitro release test (IVRT) based on recommendations provided in FDA SUPAC-SS (Scale-Up and Post-Approval Changes Non-Sterile Semisolid) guidance dated May 1997 and the IR comment sent on Nov 13, 2019. The complete method development and validation report should be submitted along with in vitro release data comparison in support of a prior approval supplement when an in vitro release comparison is needed (per SUPAC-SS).

List Submissions being reviewed (table):

Submitted data	Description	Submission Date
Module 3.2.P.2 Pharmaceutical Developments	Formulation development	09/20/2020
Module 3.2.P.5.1 Control of Drug Product	Specifications	09/20/2020
Module 1.11.1 Information Amendment: Information Not Covered Under Modules 2 to 5	Quality Information Amendment Response to Information Request 13-Nov-2019	11/29/2017

Primary Biopharmaceutics Reviewer Name and Date:**Min Li, Ph. D.**

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products

Date: 03/17/2020***Secondary Reviewer Name and Date:***

I concur with the assessment outcome.

Kimberly Raines, Ph. D.

Secondary Biopharmaceutics Reviewer
& Branch Chief
Division of Biopharmaceutics
Office of New Drug Products
Date: 03/23/2020

APPENDIX

Biopharmaceutics comments communicated to the Applicant on Nov 13, 2019:

- We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used systemically at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm²

Time (min, hr, etc.)	Sq. rt. Time	Concentration in Cell (µg/mL)	Amount in Cell (µg)	Cumulative Amount in Cell (µg)	Cumulative Diffusion (µg/cm ²)
T1					
T2					
T3					
T4					
T5					
Tn					

- Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:
 - a. Diffusion apparatus
 - b. Receptor medium selection
 - c. Membrane selection
 - d. Sampling time points
 - e. Temperature
- The IVRT method validation report should contain (but is not limited to) the following validation components:
 - a. Linearity and Range
 - b. Accuracy/Precision and Reproducibility
 - c. Mass Balance
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability
- The IVRT method's sensitivity, specificity, selectivity and robustness need should to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.



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MICROBIOLOGY

Product Information	- Indicated for the topical treatment of plaque psoriasis - 505(b)(2)
NDA Number	213422
Assessment Cycle Number	01
Drug Product Name / Strength	MC2-01 (calcipotriene/betamethasone dipropionate cream 0.005%/0.064%)
Route of Administration	Topical
Applicant Name	MC2 Therapeutics Ltd
Therapeutic Classification/OND Division	ODEIII/Division of Dermatology and Dental Products
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed

Document(s)	Date Received
NDA-213422-ORIG-1	09/20/2019
NDA-213422-ORIG-1-AMEND-6	11/29/2019
NDA-213422-ORIG-1-AMEND-11	03/10/2020
NDA-213422-ORIG-1-AMEND-12	03/20/2020
NDA-213422-ORIG-1-AMEND-14	04/27/2020
NDA-213422-ORIG-1-AMEND-15	04/28/2020
NDA-213422-ORIG-1-AMEND-16	05/01/2020
NDA-213422-ORIG-1-AMEND-20	05/26/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues: The Division of Microbiology Assessment has no deficiencies or additional comments.

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The subject drug product is a semisolid aqueous preparation for topical administration. It is a white uniform cream packaged in a 60g blind ended aluminum tube with screw cap.

Drug product composition

Ingredient	Amount (% w/w)	Amount (g/60 g tube)	Function
Calcipotriene/calcipotriol, anhydrous, USP	0.0050	0.0030	API
Betamethasone dipropionate, (b) (4), USP	0.0644	0.0386	API
Isopropyl myristate, USP	(b) (4) (b) (4)		
Mineral oil/ (b) (4) USP			
Medium-chain triglycerides, USP			
Isopropyl alcohol, USP			
Polyoxyl lauryl ether (b) (4) (4) USP			
Poloxamer (407), USP			
Polyoxyl 40 hydrogenated castor oil/ (b) (4), USP			
Carbomer interpolymer type A, USP			
Butylated hydroxyanisole/ (b) (4) USP			
Trolamine, USP			
Dibasic sodium phosphate, heptahydrate, USP			
Monobasic sodium phosphate, monohydrate, USP			
DL-A-tocopherol, USP			
Purified water, USP			

* Edited per update in the 03/20/2020 submission

Description of container closure system

Configuration	Component	Description	DMF	Manufacturer
60 g	Container	Aluminum tube	N/A	(b) (4)
	Closure	(b) (4) screw cap	N/A	

Assessment: Adequate

The Applicant has provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

The subject drug product is non-sterile. Container closure integrity testing is not required.

Assessment: Not applicable

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MICROBIOLOGY LIST OF DEFICIENCIES

Micro deficiencies are: Major Minor

The Division of Microbiology Assessment has no deficiencies or additional comments.

Primary Microbiology Assessor Name and Date:

Alifiya H. Ghadiali, Ph.D.; May 27, 2020

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

Nandini Bhattacharya, Ph.D.; May 27, 2020



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