CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215272Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 215272
Assessment 1

Drug Product Name	Vtama (tapinarof) cream, 1%
Dosage Form	Cream
Strength	1%
Route of Administration	For topical use
Rx/OTC Dispensed	Rx
Applicant	Dermavant Sciences, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission, eCTD SN 0001	05/26/2021	DS, DP, OPMA, Micro, and Biopharm
Amendment, SN 0002	06/11/2021	DP, OPMA
Amendment, SN 0004	07/28/2021	Biopharm, OPMA, Micro
Amendment, SN 0005	07/30/2021	DP, Micro
Amendment, SN 0011	10/14/2021	DP
Amendment, SN 0012	10/19/2021	OPMA
Amendment, SN 0013	10/25/2021	DP, Biopharm
Amendment, SN 0014	10/29/2021	DP
Amendment, SN 0015	11/05/2021	Biopharm
Amendment, SN 0016	05/11/2021	DP
Amendment, SN 0018	11/19/2021	OPMA
Amendment, SN 0019	12/14/2021	DP, Micro
Amendment, SN 0021	01/11/2022	DP
Amendment, SN 0022	01/26/2022	DP, Micro
Amendment, SN 0023	01/31/2022	DP, OPMA
Amendment, SN 0025	02/17/2022	DP
Amendment, SN 0027	04/04/2022	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Zhixing Shan	Donna Christner
Drug Product	Venkateswara Pavuluri	Hong Cai
Manufacturing	Youmin Wang	Yubing Tang
Microbiology	Lisa Ashmore	Julie Nemecek
Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
Regulatory Business Process Manager	Melinda Bauerlien/ Grafton Adams	
Application Technical Lead	Hong Cai/ Nina Ni	
Laboratory (OTR)	NA	NA
Environmental	Venkateswara Pavuluri	Hong Cai

QUALITY ASSESSMENT DATA SHEET

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

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Acceptable	NA	Adequate information in the NDA. Used for other approved products
	III			Adequate	02/17/2022	Reviewed by Dr. Venkateswara Pavuluri

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

Document	Application Number	Description
IND	104601	Conducted clinical studies

2. CONSULTS

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

EXECUTIVE SUMMARY

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

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging, and testing facilities have acceptable CGMP status. Labeling (package insert and container/ carton) negotiations have been completed, and in its present form, the labeling complies with the requirements under 21 CFR 201. The request for a categorical exclusion from an environmental assessment (EA) is accepted.

Thus, Dermavant's 505(b)(1) NDA 215272 for Vtama™ (tapinarof) cream, 1% submitted on May 26, 2021, is ready for APPROVAL from the OPQ perspective.

The applicant requested an expiration dating period of 36 months with adequate supporting data, which is granted for the 60-g commercial pack. The storage conditions recommended for labeling of the drug product are "**Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15 to 30˚C (59 to 86˚F). Do not freeze**."

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Dermavant has submitted this 505(b)(1) NDA for Vtama™ (tapinarof) cream, 1% for the treatment of plaque psoriasis in adults. Vtama is applied topically as a thin layer once daily to the affected skin areas.

The drug substance, tapinarof, is a novel, small molecule, nonsteroidal, therapeutic aryl hydrocarbon receptor modulating agent that has not been previously approved or marketed in the US and therefore, it is classified as a new molecular entity (NME).

Each gram of Vtama cream, 1% contains 10 mg of tapinarof in a white to off-white cream intended for topical use. Vtama cream is packaged in two configurations: 60 g in (b) (4) laminate tube with a peelable sealed membrane and a (b) (4) closure for commercial use; and 2 g in an aluminum tube with a sealed membrane and a membrane piercing (b) (4) closure for use as the physician sample.

A 36-month expiration dating period for the drug product when stored at 20ºC to 25ºC has been granted for the 60-g commercial pack. An (b) (4)-month expiration dating period for the drug product when stored at 20ºC to 25ºC has been granted for the 2-g physician samples.

Proposed Indication(s) including Intended Patient Population	For the tropical treatment of plaque psoriasis in adults
Duration of Treatment	(b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Tapinarof is a white to pale brown olefinic compound with the molecular formula of $C_{17}H_{18}O_2$ and molecular weight of 254.32. Tapinarof has no chiral centers. Tapinarof is an olefinic compound that contains one double bond in the trans configuration, which is proven by single crystal X-ray crystallography. Four anhydrous crystalline forms have been identified to date. Form (b) (4) has been used throughout the development. Tapinarof is practically insoluble (≤ 0.1 mg/mL) in water and freely soluble in methanol, ethanol, and acetone (> 200 mg/mL).

Tapinarof drug substance is manufactured using (b) (4) The qualities of the starting material and all the (b) (4) intermediates are controlled against their respective specifications. The reactions and the manufacturing process are well established and have been shown to work well for both registration and commercial batches.

The chemical structure of tapinarof has been adequately defined by single crystal X-ray crystallography, powder X-ray diffraction, proton and carbon NMR spectroscopy, mass spectrometry, as well as infrared spectroscopy.

The applicant has proposed adequate drug substance specification, which includes all critical drug substance attributes that affect the manufacturing and quality of the drug product. The proposed specification includes the following tests: description by visual inspection, identification by IR,

tapinarof content by HPLC, drug related impurities by HPLC, (b) (4) , and water content by Karl Fischer. The applicant has provided adequate risk assessment for not controlling nitrosamine, elemental impurities, and potential mutagenic impurities in the drug substance. Lack control of particle size and polymorphic form for the drug substance is also acceptable (b) (4) The applicant has also provided adequate justification on not controlling the following in the drug substance specification: microbial, (b) (4) , and residue on ignition.

Based on the stability data obtained to date, a retest period of (b) (4) months can be granted for the drug substance, when stored at (b) (4) .

The drug substance reviewer Dr. Zhixing Shan finds the information on the drug substance manufacturing process, characterization, specification, container closure system, and stability are all satisfactory to support the approval of the NDA. See the relevant IQA Chapter below for details.

Drug Product: Adequate

The proposed drug product, VTAMA™ (tapinarof) cream, 1% for topical use is an (b) (4) emulsion formulation supplied either in 60-g (b) (4) laminate tube for commercial use, or in 2-g aluminum tube as physician samples.

Tapinarof cream, 1% contains medium chain triglycerides (b) (4) along with (b) (4) (diethylene glycol monoethyl ether and propylene glycol) (b) (4) in the final formulation. (b) (4) polysorbate 80, polyoxyl 2 stearyl ether (b) (4)), and polyoxyl 20 stearyl ether (b) (4) purified water. Emulsifying wax (b) (4) Other (b) (4) excipients selected are benzoic acid (b) (4) , citric acid/ sodium citrate (b) (4) , butylated hydroxytoluene (b) (4) , and disodium edetate (b) (4) . All excipients are compendial grade. Except for purified water and (b) (4) , all other excipients listed in Inactive Ingredient Database (IID) are used at or below the levels present in approved drug products for the type of formulation and route of administration. The Pharm Tox reviewer, Dr. Cindy (Xinguang) Li, via email, dated 12/23/2021 confirmed that the level of (b) (4) has been adequately justified by the pivotal repeat-dose dermal toxicity studies.

The quality tests included in drug product regulatory specification are in line with the USP <3> *Topical and Transdermal Drug Products – Product Quality Tests and* therein are deemed adequate for release testing of drug product batches, when combined with in-process tests (e.g., (b) (4) Justification provided for excluding certain required tests from drug product specification (i.e., elemental impurities, (b) (4) at release, and weight loss on shelf-life testing) is acceptable. Although the applicant did not provide risk assessment for potential nitrosamine contamination in the drug product, this issue will not be communicated to the applicant based on the following risk assessments: first, potential risk of nitrosamine contamination in the drug substance has been adequately assessed (refer to drug substance review for details); second, this cream formulation contains relative low quantities of excipients and each excipient with low amine and/ or nitrite content; third, the product formulation contains (b) (4) butylated hydroxytoluene and (b) (4) EDTA; fourth, the applicant provided risk assessment of nitrosamine contamination (b) (4) in the comparability protocol in which a change of (b) (4) is proposed; and fifth, the proposed drug product is a cream for topic use (b) (4).

The acceptance criteria and/ or limits proposed for various individual tests in the drug product regulatory specification are supported by data for the registration batches at release and on stability in both 60-g and 2-g tube packs. The limits proposed for (b) (4) of tapinarof ((b) (4)) content, at NMT (b) (4) % at release and end of shelf-life are supported by qualification through pivotal repeat-dose dermal toxicity studies on tapinarof drug product, which was confirmed by Pharm Tox reviewer, Dr. Cindy Li, via email, dated 02/17/2022. None of the other drug-related impurities/ degradants detected in drug product batches exceed the ICH Q3B(R2) recommended identification threshold for a drug with a maximum daily dose in the range of >10 mg - 2 g, and thus the limit of no more than (b) (4) % proposed for drug-related unspecified impurities is justified.

The HPLC analytical methods used for identification, assay, tube content uniformity, and drug-related impurities of tapinarof; as well as benzoic acid and butylated hydroxytoluene content in drug product batches (b) (4) are adequately validated and deemed suitable. Use of bracketing/ matrixing approach, by testing cream batches containing 0.5% and 3% of tapinarof for certain test parameters for tapinarof cream, 1%, during validation of analytical methods is acceptable. Globule size (Dv50 and DV90) values are measured by adopting USP <429> *Light Diffraction Measurement of Particle Size*.

The container closure system (CCS) components selected for packaging of both commercial and physician samples are deemed adequately qualified, which also used for packaging other approved drug products. The proposal for not monitoring the leachables into drug product as part of batch release and stability testing is acceptable based on the provided risk assessment. The seal integrity is evaluated and controlled as part of (b) (4) for both 60-g (b) (4) and 2-g Al tubes. No leakage of cream from the (b) (4) or Al tubes were recorded for the primary stability batches, at any of the time points and storage conditions. DMF (b) (4) was referenced to support the use of (b) (4) which was reviewed and found adequate by Dr. Venkateswara Pavuluri on 02/17/2022.

The proposed shelf-life of 36 months for drug product in 60-g (b) (4) laminate tubes is supported by the stability data provided for three registration batches, up to 36 months at 25°C/60% RH and 30°C/75% RH storage conditions. The shelf-life of (b) (4) months proposed in 2-g aluminum tubes is supported by stability data provided for three registration batches, up to 12 months' time point at 25°C/60% RH and 30°C/75% RH storage conditions and extrapolation of the stability data for critical quality attributes per ICH Q3E. The storage conditions recommended for labeling of the drug product are "**Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15 to 30˚C (59 to 86˚F). Do not freeze**."

The request for categorical exclusion from filing an environmental impact assessment under 21 CFR § 25.31(b) is acceptable.

Via email, dated 11/01/2021, Joel Hathaway, Ph. D. from Office of Life Cycle Product (OLDP) confirmed that the proposed reduced reporting category in the comparability protocol, for change of (b) (4) in the Annual Report is acceptable.

The drug product reviewer, Dr. Venkateswara Pavuluri finds the information on the tapinarof drug product is adequate to support the approval of the NDA. See the relevant IQA Chapter below for details.

Labeling: Adequate

During the assessment of the labeling (prescribing information (PI), and container/ carton labels), several deficiencies were identified. All deficiencies are now adequately resolved. Refer to the relevant IQA Chapter below by Dr. Venkateswara Pavuluri for the detailed evaluations.

Manufacturing: Adequate

The manufacturing process involve (b) (4) [redacted]. All process parameters are established based on experimental design studies and the operating range of CPPs including (b) (4) [redacted].

All manufacturing facilities listed in table below are found adequate.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4) [redacted]		Drug substance manufacture, packaging, release testing, and stability testing || 356h Status: Pending CSN	Approve - Based on Previous History
		Drug product manufacture, packaging (primary and secondary), release testing, and stability testing || 356h Status: Pending OIN	Approve - Based on Previous History
		In-vitro Release testing (IVRT) || 356h Status: Pending LCP	Approve - Based on Previous History
		Warehouse storage for tapinarof drug substance prior to manufacture. || 356h Status: Pending CSN	No Evaluation Necessary

The Process and Facility reviewer Dr. Youmin Wang finds the information on the tapinarof drug product process and facilities is adequate to support the approval of the NDA. See the relevant IQA Chapter below for details.

Biopharmaceutics: Adequate

The formulation used in pivotal Phase 3 clinical studies is the same as the proposed commercial formulation. Therefore, no in vitro or in vivo formulation bridging study is needed.

The applicant developed and validated an in-vitro release testing (IVRT) method using a modified Franz cell system. The proposed IVRT method is acceptable. The Biopharmaceutic reviewer, Dr. Kalpana Paudel noted that an increase in in-vitro drug release with age of the product was observed during stability. All other physico-chemical properties, including appearance, viscosity, degradants, (b) (4) globule size, and potential crystallization of tapinarof were not changed when stored at the long-term storage conditions of 25ºC. This issue was communicated to the drug product, Clinical, and Clinical Pharmacology teams. Although root cause was further investigated via additional communications with the applicant during this review cycle, no direct root cause could be found. Since a

wider age range of the drug products have been used in the Phase 3 clinical studies so the up-trending increase of in-vitro drug release with age of the product deems qualified in the proposed clinical studies, which was confirmed by the reviewer from Office of Clinical Pharmacology (OCP) via email, dated 01/05/2022. Thus, although in absence of direct causality between upward trend of drug release and other in vivo parameters, in vitro drug release method and acceptance criteria, as proposed by the applicant appears acceptable from the Biopharmaceutics perspective. However, the applicant has been requested to do IVR testing along with other critical quality attributes on first three commercial batches throughout the stability period in an IR dated 10/29/2021 sent by the drug product reviewer for which the applicant has agreed. Once the IVRT data as per the IR are reviewed by the FDA, further action in this regard should be taken.

The Biopharmaceutic reviewer Dr. Kalpana Paudel finds the Biopharmaceutical information on the tapinarof drug product is adequate to support the approval of the NDA. See the relevant IQA Chapter below for details.

Microbiology (if applicable): Adequate

The drug product is a non-sterile, (b) (4), topical cream, packaged in a multidose 60-g tube (commercial pack) or 2-g tube (physician sample). The critical aspects from the microbiology perspective are microbiological release testing and (b) (4). These aspects were reviewed and found acceptable.

The applicant has provided sufficient data to support the microbial limits method suitability for TAMC and TYMC per USP <61>, *S. aureus* and *P. aeruginosa* per USP <62>, and BCC per USP <60>. The applicant has also provided sufficient data to support the (b) (4) listed in the stability specification and within the required pH range.

The Microbiologic reviewer Dr. Lisa Ashmore finds the micro information on the tapinarof drug product is adequate to support the approval of the NDA. See the relevant IQA Chapter below for details.

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**

Assay and tube content uniformity	(b) (4)	M	(b) (4)	Low	None
Globule size distribution		M		Low	None
Crystallization of the drug		M		Low	None

			(b) (4)		
Drug-related substances/ degradation products	Drug (b) (4) is prone to oxidative and (b) (4) based on forced degradation studies.	H		Low	None
In vitro drug release (IVRT)	Drug (b) (4) may precipitate overtime, affecting its release from the formulation.	M		Low	The applicant has been requested to do IVR testing along with other critical quality attributes on first three commercial batches throughout the stability period.
Microbial control	The drug product is a non-sterile, (b) (4) topical cream.	M		Low	None
Extractable/leachable	The drug product contains (b) (4)	M		Low	None

	(b) (4)				

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies *(Specify discipline, such as Environmental)*

None

Application Technical Lead Name and Date:

Nina Ni, Ph. D., 04/08/2022

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

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION (As submitted in SN 0008; Date 23-AUG-2021)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	Delete (b) (4) included after drug product name
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	Terminology used for (b) (4) , shall be deleted.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not a tablet.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not injectable.
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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)	N/A	Cream, doesn't require special preparation.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products*	N/A	Not a parenteral product.

must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not injection.

Section 11 (DESCRIPTION)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Inadequate	To be clear, the established name typically is presented next to the proprietary name at least once in section 11 as the following: "VTAMA (tapinarof) cream …"
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Inactive ingredients shall be listed by USP/NF names (where available) in alphabetical order, per USP <1091>.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral product.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No Alcohol present
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Inadequate	Not provided. Add the following sentence: Tapinarof is (b) (4) aryl hydrocarbon receptor (AhR) (b) (4).
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	N/A	Not provided.

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	No promotional statements.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	No Monograph in USP

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Inadequate	Add the statement "**Each gram of VTAMA Cream contains 10 mg of tapinarof**."
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Inadequate	Revise the statements as follows. VTAMA (tapinarof) Cream, 1% is a white to off-white cream. Each gram of VTAMA Cream contains 10 mg of tapinarof. It is supplied in the following size: 60g **laminated tubes**: NDC 81672-5051-01
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	Statement "Do not freeze." included. Also include the statement **"Protect from exposure to excessive heat."**

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

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	Revise the storage conditions as "Store at 20°**C** to 25°C (68°**F** to 77°F); with excursions permitted **between** 15°C and 30°C (59°**F** and 86°F) (b) (4) [redacted] "Discard any unused cream in the tube after 30 days of initial use"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	Not Child resistant tube.

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 parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review 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.

Not Applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Submitted in SN 0001, Date 25-MAY-2021

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Inadequate	Add the statements "**Protect VTAMA Cream from exposure to excessive heat**." and "Discard any unused cream in the tube after 30 days of initial use"
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	Inactive ingredients shall be listed by USP/NF names (where available) in alphabetical order, per USP <1091>.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Inadequate	To include street address before City name.

Deficiencies listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

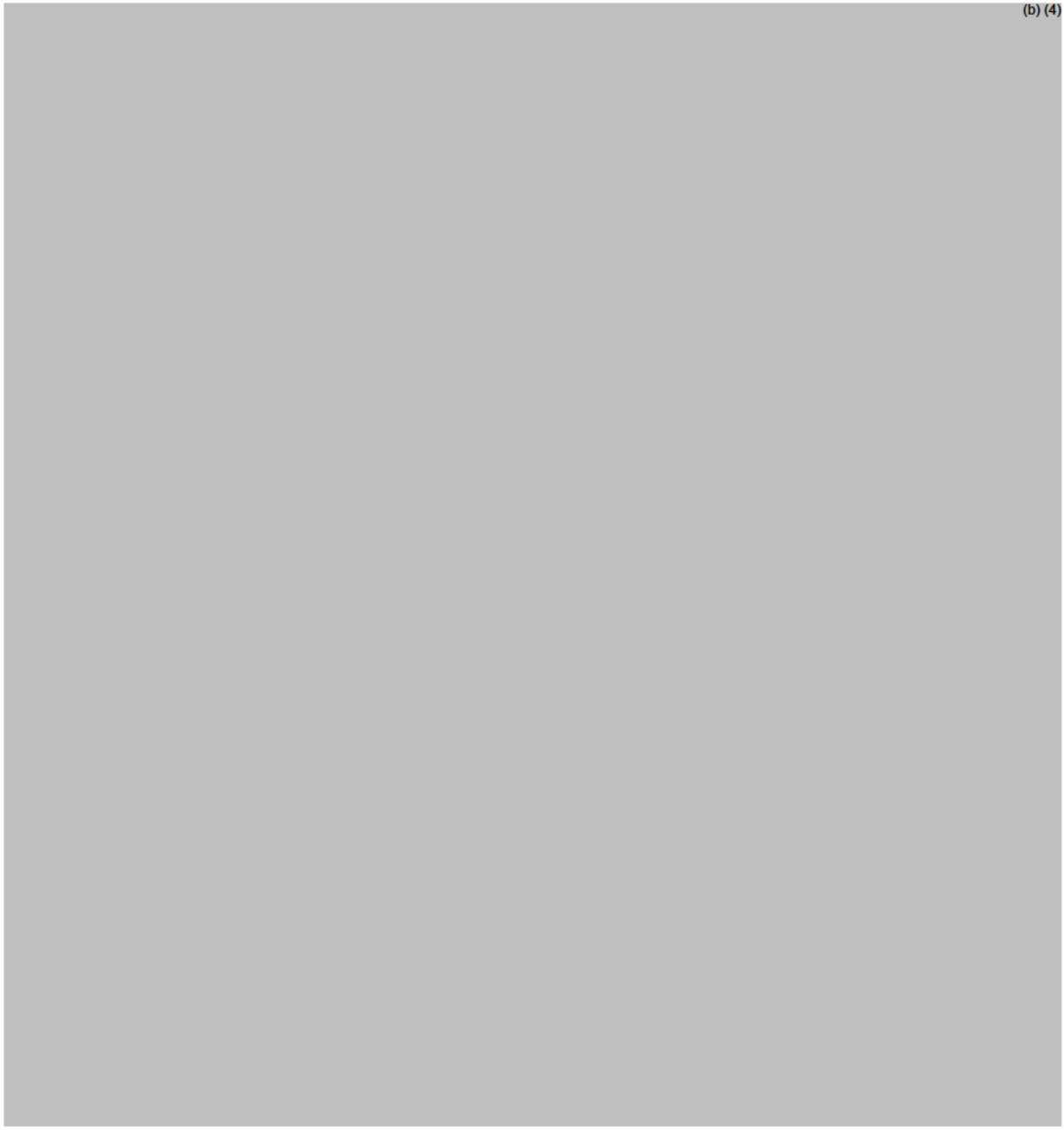
[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

(Submitted in SN 0001 Date 26-MAY-2021)

3.1 Container Labels

(b) (4)



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

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Inadequate	Deferred to DMEPA for the requirements for font size and prominence.
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	Rx may be moved away from the NDC number, to the left (bottom or top) side of main panel.
NDC	Adequate	
Lot number and expiration date	Inadequate	The format of Lot number and expiry date should be included on both commercial and sample packs, and compliant with 21 CFR 201.17. Per 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. Provide the format to be used for expiration dating, i.e., DD/MM/YYYY or MMMYYYY.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Revise the text as follows: - Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to between 15°C to and 30°C (59°F to and 86°F). - Do not freeze. - **Protect from exposure to excessive heat.** **- Discard any unused cream in the tube after 30 days of initial use.** - (b) (4)

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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Inadequate	The bar code should have the NDC number as linear numerical data, leaving blank spaces (0 xxxx X marks) is not acceptable.

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	Inadequate	Inactive ingredients shall be listed by USP/NF names (where available) in alphabetical order per USP <1091> on the carton and as well container label, when the available space allows.

Assessment of Carton and Container Labeling: Inadequate.

See under "Items for Additional Assessment" for details

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information

HIGHLIGHTS

Product Title in Highlights

1. Revise the Title deleting (b) (4) included after drug product name, (b) (4).

Dosage forms and strengths

2. Revise the text deleting [redacted] (b) (4) .

11 DESCRIPTION

3. Revise / add the statements in respective paragraphs as indicated below:
Paragraph 1: VTAMA (tapinarof) Cream [redacted] (b) (4) contains tapinarof as the active ingredient. Tapinarof is [redacted] (b) (4) aryl hydrocarbon receptor (AhR) [redacted] (b) (4) .

Paragraph 2: Tapinarof is a white to pale brown powder. Chemically, tapinarof is 3, 5-dihydroxydihydroxy-4-isopropyl-*trans*-stilbene, also known as (E)-2-isopropyl-5-styrylbenzene-1,3 diol, with the empirical formula C17H18O2, a molecular weight of 254.32, and the following structural formula.

Paragraph 3:

Add "Each gram of VTAMA Cream for topical use contains 10 mg of tapinarof in a white to off-white cream." *as sentence 1 and revise the subsequent statement on inactive ingredients by listing all inactive ingredients using USP/NF names (where available) in alphabetical order, per USP <1091>.*

16 HOW SUPPLIED/STORAGE AND HANDLING

4. *Revise the text as*: VTAMA (tapinarof) Cream, 1% is a white to off-white cream. Each gram of VTAMA Cream contains 10 mg of tapinarof. It is supplied in laminated tubes in the following size:

60 laminated tubes: NDC 81672-5051-01

5. *Revise the storage statements adding the following statement*:

- Protect from exposure to excessive heat.
- Discard any unused cream in the tube after 30 days of initial use

Storage and Handling:

- Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).
- Do not freeze.
- Protect from exposure to excessive heat.
- Keep out of reach of children.

Patient Labeling:

6. *Revise product name as* "VTAMATM (tapinarof) Cream, (Vee-TAM-uh), for topical use".
7. *Add the statement* "Protect VTAMA Cream from exposure to excessive heat." under '**How should I store VTAMA Cream?**'

8. *Include Street Address* "3780 Kilroy Airport Way," *prior to the City name under "***Marketed by***" section.*

Container and Carton Labels (Applicable to both Commercial and Sample Packs):

9. Per 21 CFR 201.17, unless it is easily legible through such outer package, expiration dating must be displayed on both the immediate container label and carton for a drug product including the sample size tubes. Provide revised text for container labels and carton, indicating the location for placing Lot number and Expiration date.

10. Per 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. Provide the lot number format to be used on the drug product labels. Also provide the format to be used for expiration dating, i.e., DD/MM/YYYY or MMMYYYY.

11. Per 21 CFR 201.25(c), at a minimum the appropriate National Drug Code (NDC) number should be in a linear bar code that meets European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standards or another standard or format that has been approved by the Food and Drug Administration. Provide revised text for container labels and carton, inserting the NDC number in place of blank spaces under the barcode.

12. Add the statement "**Discard any unused cream in the tube after 30 days of initial use**" on the container and carton labels.

13. Add the statement "**Protect from exposure to excessive heat.**" under the subhead "Storage" on carton and container label (where space permits).

14. Revise the inactive ingredients listing by using USP/NF names (where available) in an alphabetical order, per USP <1091>.

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated under the "ITEMS FORADDITIONAL ASSESSEMNT" above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.,

Chemist, DNDC II/ONDP/OPQ
02-17-2021

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

Hong Cai, Ph. D.,
Chief, Branch 4; DNDC II/ONDP/OPQ

Venkateswara Pavuluri

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Hong Cai

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Date: 2/19/2022 10:32:54AM
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Memorandum

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

Date: **05-APR-2022**

From: **Venkateswara R. Pavuluri, Ph.D., R. Ph.**
Drug Product Reviewer
DNDP II
Office of New Drug Products

Through: **Hong Cai, Ph.D.**
Branch Chief, Br. 4/DNDP II
Office of New Drug Products

To: **CMC Labeling Review of NDA 215272 for VTAMA®**
Subject: Final Recommendation – APPROVAL

At the time when Original Labeling Review of NDA 215272 was completed, on 02-17-2022, this NDA was not recommended for approval 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective due to deficiencies listed below. The NDA for this drug product was otherwise complete and adequate from the drug product perspective, per the review dated 02-11-2022.

Labeling/Label Deficiencies identified in Labeling review on 02-17-2022:

Prescribing Information

HIGHLIGHTS

Product Title in Highlights

1. *Revise the Title deleting* (b) (4) *included after drug product name,* (b) (4).

Assessment of Applicant's Response: **Adequate.**

Dosage forms and strengths

2. *Revise the text deleting description of the cream, i.e.,* (b) (4).

Assessment of Applicant's Response: **Adequate.**

11. DESCRIPTION

3. *Revise / add the statements in respective paragraphs as indicated below*:

Paragraph 1: VTAMA (tapinarof) Cream (b) (4) contains tapinarof as the active ingredient. Tapinarof is (b) (4) aryl hydrocarbon receptor (AhR) (b) (4).

Assessment of Applicant's Response: **Adequate.**

Paragraph 2: Tapinarof is a white to pale brown powder. Chemically, tapinarof is 3, 5-dihydroxydihydroxy-4-isopropyl-*trans*-stilbene, also known as (E)-2-isopropyl-5-styrylbenzene-1,3 diol, with the empirical formula $C_{17}H_{18}O_2$, a molecular weight of 254.32, and the following structural formula.

Assessment of Applicant's Response: **Adequate.**

Paragraph 3: *Add* "Each gram of VTAMA Cream for topical use contains 10 mg of tapinarof in a white to off-white cream." *as sentence 1 and revise the subsequent statement on inactive ingredients by listing all inactive ingredients using USP/NF names (where available) in alphabetical order, per USP <1091>.*

Assessment of Applicant's Response: **Adequate.**

16 HOW SUPPLIED/STORAGE AND HANDLING

4. *Revise the text as*: VTAMA (tapinarof) Cream, 1% is a white to off-white cream. Each gram of VTAMA Cream contains 10 mg of tapinarof. It is supplied in laminated tubes in the following size:

   60 laminated tubes: NDC 81672-5051-01

Assessment of Applicant's Response: **Adequate.**

5. Revise the storage statements adding the following statements:

Storage and Handling:

- Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).
- Do not freeze.
- Protect from exposure to excessive heat.
- Keep out of reach of children.
- Discard any unused cream in the tube after 30 days of initial use

Assessment of Applicant's Response: **Adequate.**

Reviewer's Note: Applicant's justification for not including the statement "Discard any unused cream in the tube after 30 days of initial use ." is acceptable.

Patient Labeling:

6. *Revise product name as* "VTAMA™ (tapinarof) Cream, (Vee-TAM-uh), for topical use".

Assessment of Applicant's Response: **Adequate.**

7. *Add the statement* "Protect VTAMA Cream from exposure to excessive heat." under '**How should I store VTAMA Cream?'**

Assessment of Applicant's Response: Adequate.

Reviewer's Note: Applicant's justification for not including the statement "Discard any unused cream in the tube after 30 days of initial use ." is acceptable.

8. *Include Street Address* "3780 Kilroy Airport Way," *prior to the City name under "***Marketed by***" section.*

Assessment of Applicant's Response: **Adequate.**

<u>Container and Carton Labels (Applicable to both Commercial and Sample Packs)</u>:

9. Per 21 CFR 201.17, unless it is easily legible through such outer package, expiration dating must be displayed on both the immediate container label and carton for a drug product including the sample size tubes. Provide revised text for container labels and carton, indicating the location for placing Lot number and Expiration date.

Assessment of Applicant's Response: **Adequate**.

10. Per 21 CFR 201.18, the lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. Provide the lot number format to be used on the drug product labels. Also provide the format to be used for expiration dating, i.e., DD/MM/YYYY or MMMYYYY.

Assessment of Applicant's Response: **Adequate.**

11. Per 21 CFR 201.25(c), at a minimum the appropriate National Drug Code (NDC) number should be in a linear bar code that meets European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standards or another standard or format that has been approved by the Food and Drug Administration. Provide revised text for container labels and carton, inserting the NDC number in place of blank spaces under the barcode.

Assessment of Applicant's Response: **Adequate.**

12. Add the statement "**Discard any unused cream in the tube after 30 days of initial use**" on the container and carton labels.

Assessment of Applicant's Response: **Adequate.**

Reviewer's Note: Applicant's justification for not including the statement "Discard any unused cream in the tube after 30 days of initial use ." is acceptable.

13. Add the statement "**Protect from exposure to excessive heat.**" under the subhead "Storage" on carton and container label (where space permits).

Assessment of Applicant's Response: **Adequate.**

14. Revise the inactive ingredients listing by using USP/NF names (where available) in an alphabetical order, per USP <1091>.

Assessment of Applicant's Response: **Adequate.**

Recommendation:

The CMC label/labeling issues identified in the labeling review have been satisfactorily resolved as reproduced in attachments below. This application is recommended for APPROVAL from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.,
Drug Product Reviewer
DNDP II, ONDP

Hong Cai, Ph. D.,
Branch Chief, Br4/DNDP II, ONDP

Venkateswara Pavuluri

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Hong Cai

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Date: 4/05/2022 03:49:40PM
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BIOPHARMACEUTICS

Product Background:

NDA: NDA 215272-ORIG-1

Drug Product Name / Strength: Tapinarof cream/1.0%

Indication: Topical treatment of plaque psoriasis in adults

Route of Administration: Topical

Applicant Name: Dermavant Sciences GMBH

Review Recommendation: The submission is **ADEQUATE** from Biopharmaceutics perspective with key findings summarized below:

In Vitro Release Test (IVRT) and Acceptance Criteria

The Applicant developed and validated an IVRT method using a modified Franz cell system. The proposed IVRT method is acceptable. It is noted that an increase in in-vitro drug release with age of the product was observed during stability. Chemistry, Clinical and Clinical Pharmacology teams were informed, and root cause was further investigated via additional communications with the applicant. However, no direct root cause could be found. In absence of direct causality between upward trend of drug release and other in vivo parameters, in vitro drug release method and acceptance criteria, as proposed by the applicant and described below, are acceptable from Biopharmaceutics perspective. The Applicant has been requested to do IVR testing along with other critical quality attributes on first three commercial lots throughout the stability period in an IR dated Oct. 29, 2021 sent by DP reviewer which the Applicant has agreed. Once the IVR data as per this IR are reviewed by the FDA, further action in this regard will be taken.

The submission is **ADEQUATE** from Biopharmaceutics perspective.

The following IVRT method and acceptance criteria has been approved for tapinarof cream 1.0%.

Apparatus	Stir rate RPM	Receptor medium/Temperature	Membrane type	Acceptance criteria
Franz cell system	600	DMSO:IPA:H_2O (60:20:20 v/v/v) / 32°C	Nylon, 0.45 µm pore size, 25 mm diameter	Release: (b) (4) $\mu g/cm^2/min^{1/2}$ End of Shelf Life: Not greater than (b) (4) $\mu g/cm^2/min^{1/2}$

Formulation development and bridging

The formulation used in pivotal Phase 3 clinical studies is same as the proposed commercial formulation. Therefore, no in vitro or in vivo formulation bridging study is needed.

Recommendation
From Biopharmaceutics perspective, NDA 215272 for Tapinarof 1.0% cream is adequate.

List of Submissions being reviewed:
Sequence 0001
Sequence 0004
Sequence 0013
Sequence 0015

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: Not relevant for cream formulation.

1. Composition of proposed drug product
The composition of Tapinarof 1.0% cream, along with the functions and quality standards of the components, are shown in Table 1 below.

Table 1: Composition of Tapinarof 1.0% cream

Component	Quantity (% w/w)	Function	Reference to Standard
Tapinarof	1.00	Active	In House (Dermavant)[a]
Water, Purified	(b) (4)		USP-NF
Sodium Citrate Dihydrate			USP-NF
Disodium Edetate			USP-NF
Citric Acid Monohydrate			USP-NF
Medium Chain Triglycerides			USP-NF
Propylene Glycol			USP-NF
Emulsifying Wax			USP-NF
Diethylene Glycol Monoethyl Ether			USP-NF
Polyoxyl 2 Stearyl Ether			USP-NF
Polysorbate 80			USP-NF
Polyoxyl 20 Stearyl Ether			USP-NF
Benzoic Acid			USP-NF
Butylated Hydroxytoluene			USP-NF

a. Details of the specification of the active ingredient are provided in Section 3.2.S.4.1 Specifications.
USP-NF = United States Pharmacopoeia - National Formulary.

2. IVRT method and acceptance criteria

IVRT method

The Applicant has developed an IVRT method for Tapinarof 1.0% cream using Franz diffusion cell system in accordance with USP<1724> in order to support future testing of product stability, quality control release, and lot/product comparison as required by FDA's SUPAC-SS (Guidance for Industry for Non- Sterile Semisolid Dosage Forms).

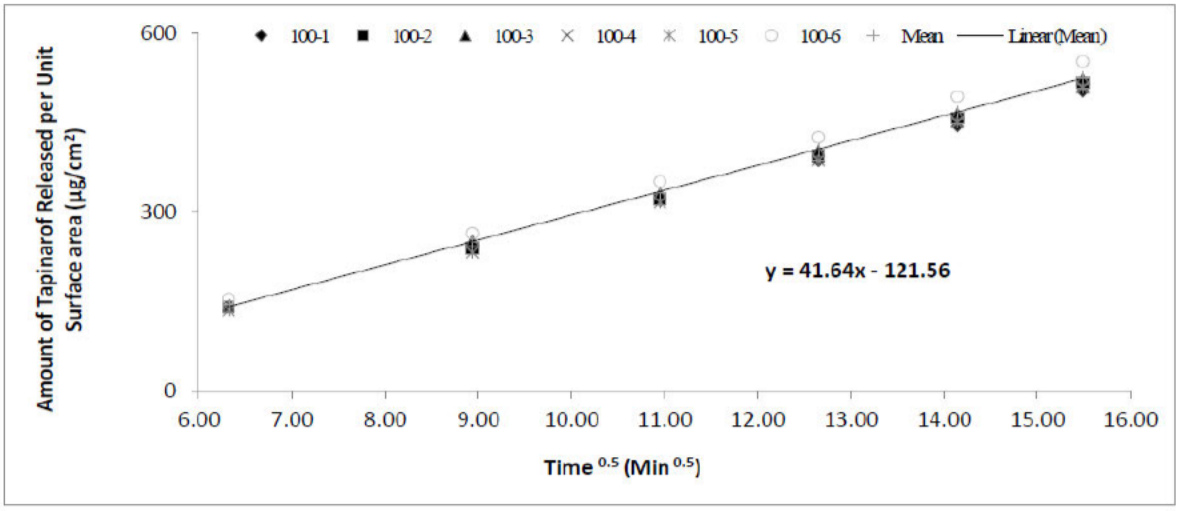
The method is fully validated. The details of the analytical procedure and method validation are provided in the links below:

\\CDSESUB1\evsprod\nda215272\0001\m3\32-body-data\32p-drug-prod\dmvt-505(tapinarof)-cream\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedure.pdf

\\CDSESUB1\evsprod\nda215272\0001\m3\32-body-data\32p-drug-prod\dmvt-505(tapinarof)-cream\32p5-contr-drug-prod\32p53-val-analyt-proc\6-validation-analytical-procedures_ivrt.pdf

A typical release rate profile of Tapinarof Cream, 1% is shown below.

Figure 1: Tapinarof Cream, 1% Typical Release Rate Profile



100-1 through 100-6 represent the individual points collected from Franz cell vessels 1 through 6 using the tapinarof cream 1% formulation.
"+" represents the mean of the individual values at each time point.
The "Linear (Mean)" line is the linear fit through the mean at each time point.

(b) (4)

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(b) (4)

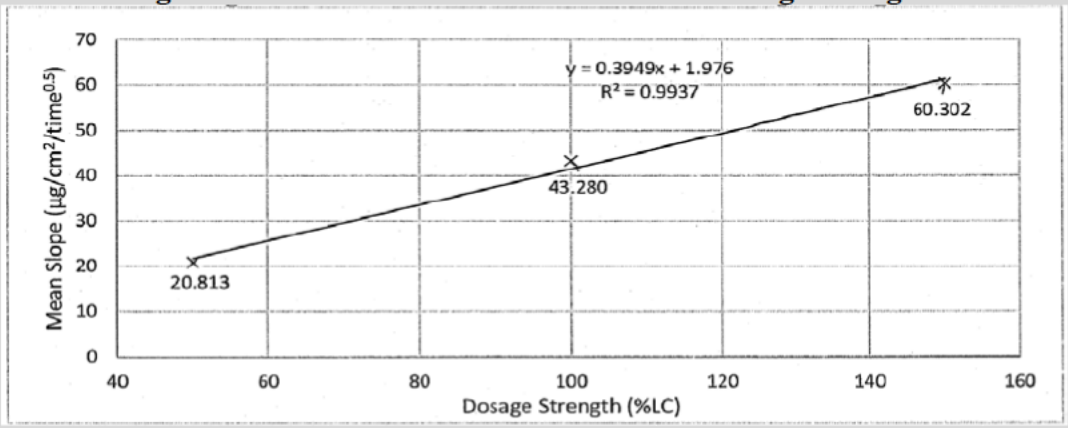
[redacted]

IVRT method's discrimination power

Effect of changes in dosage strength (sensitivity and specificity)

The sensitivity of the method to detect a change in the release rate as a function of the amount of Tapinarof in the formulation was evaluated by comparing the rate of release for formulations of 50%, 100% and 150% strengths. As seen in the figure below, the method is sensitive for changes in the amount of drug substance present in the formulation.

Figure 2: IVRT Release Rates of Different Dosage strengths



Effect of changes in formulation composition (selectivity)

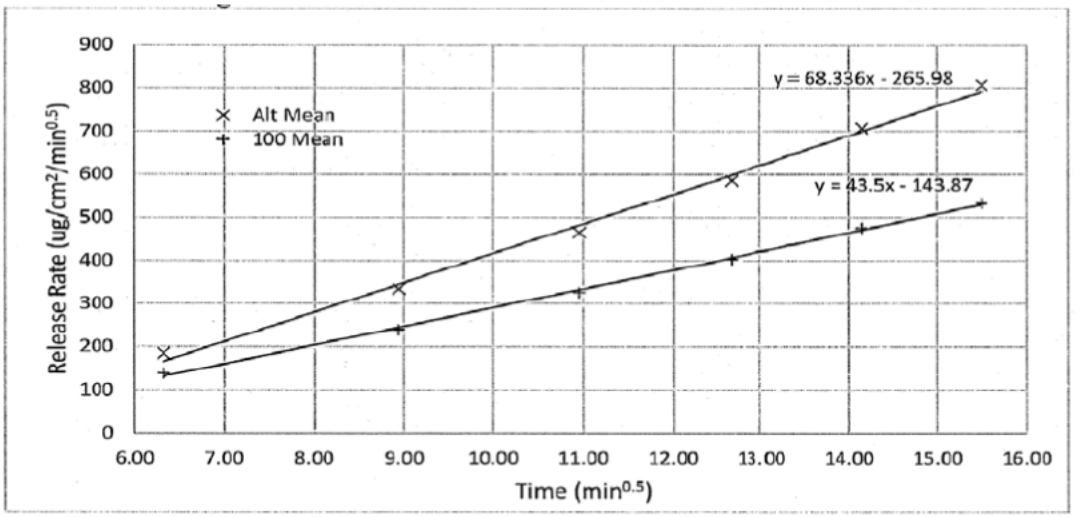
The effect of change in the concentration of key excipient was investigated, with the altered lot containing [redacted] (b) (4), as opposed to [redacted] (b) (4) content of the exhibit lot. The mean release rates of the altered lot compared to that of the Exhibit lot is shown in the table and figure below.

Table 4: Sensitivity of IVRT to Different Formulations

Sample	Lot	Mean Slope (µg/cm²/time^0.5)	%Difference	Mean Cumulative Released Amount (mg)	%Difference
[redacted] (b) (4)	833680	43.280	NA	532.810	NA
[redacted] (b) (4)	833703	66.915	43.1	807.128	51.5
Criteria	%Difference in mean release rate and cumulative released amount more than ± [redacted] (b) (4) %				
Status	All results show significant difference				

Reference: LNB-20-017/p.36 [6]

Figure 3: Comparison of Release Rates of Altered and Target Formulations



Mass Balance

The mass balance evaluation was performed for all dosage strengths and altered lot by extracting the sample remaining on each membrane at the end of the IVRT test and comparing with the total amount applied to the membrane. As most of the active amount was accountable for all sample loads, good mass balance was obtained and the % recoveries ranged from (b) (4)% to (b) (4)% (Table 5), which were well within the limit of 80-120%. It is also shown that the final released amount at T=240 min for all dosage strengths was in the range of (b) (4)% to (b) (4)% of the total applied API amount, thus being well below the limit of (b) (4)% for IVRT.

Table 5: Summary of Amount Released at T=240 min and Mass Balance (50,100,150%LC and Altered Formulation

Sample	Applied Sample(mg)	Applied API (mg)	Released amount (mg)	%Release vs. Applied	Extraction Concentration (µg/mL)	Extraction Amount (mg)	% Recovery (Mass Balance)
50%-1	(b) (4)						
50%-2							
50%-3							
100%-1							
100%-2							
100%-3							
150%-1							
150%-2							
150%-3							
Mean	607.8			15.2			100.5
%RSD	4.6			5.4			0.6
Alt%-1	(b) (4)						
Alt%-2							
Alt%-3							
Mean	569.1			25.1			99.6
%RSD	1.7			5.7			2.5

Reference: Laboratory Notebook, LNB-20-017/p. 35-36 [6]

IVRT acceptance criteria

The Applicant proposed the following acceptance criteria based on the variability in the measurement system, data from recently manufactured batches, and stability data on batches of tapinarof cream, 1% tested to date. The Applicant noted that data are not available for clinical batches at the initial time point. This method was added based on FDA feedback and was not fully validated until the 3-month time point.

Acceptance Criteria at release: (b) (4) to (b) (4) $\mu g/cm^2/ min^{1/2}$
Acceptance Criteria at end of shelf life: not greater than (b) (4) $\mu g/cm^2/ min^{1/2}$

The Applicant provided data to support the proposed limit for IVRT at the time of batch release and at the end of shelf life. The IVRT ranges are between (b) (4) and (b) (4) for batches tested within three months of manufacture and increase to (b) (4) to (b) (4) on stability for samples stored at 25°C/60% RH. IVRT data for two development batches and three process qualification batches that were tested soon after manufacture are presented in Table 6.

Table 6: IVRT data for Tapinarof Cream, 1% Batches Tested within 3 Months of Manufacture

Batch	Date of Manufacture	Date IVRT measured	IVRT $\mu g/cm^2/min^{(0.5)}$
833680[a]	FEB-2020	MAY-2020	(b) (4)
AG6S[b]	FEB-2021	MAR-2021	
AG6Y[b]	FEB-2021	MAR-2021	
AG7A[b]	FEB-2021	MAR-2021	

a. Lab scale batch manufactured to support IVRT method development and validation.
b. Triplicate testing across the filling batch was conducted.

IVRT data for batches made for Phase 3 clinical studies are presented in Table 7. Samples were tested as soon as the IVRT method was validated.

Table 7: IVRT data for Phase 3 Clinical Batches

Batch	Date of Manufacture	Date Tested	Age at time of analysis (months)	IVRT $\mu g/cm^2/min^{(0.5)}$
C793583	NOV-2016	AUG-2020	45	(b) (4)
C793606[a]	NOV-2016	AUG-2020	45	
C793607[a]	NOV-2016	AUG-2020	45	
C796592[a]	JAN-2017	JUL-2020	42	
C796593[a]	JAN-2017	JUL-2020	42	
P64P	APR-2019	JUL-2020	15	
P87N	APR-2019	JUL-2020	15	
P87P	APR-2019	JUL-2020	15	

a. Produced for Phase 3 studies, but not used in trials.
Note: All samples were packaged in 30-g Aluminum tubes and stored at controlled ambient warehouse conditions (15 to 30°C).

IVRT data are presented in Table below for the 60-g (b) (4) primary registration batches. The data for the 60-g (b) (4) tube package are limited to the 30-month and 36-month time points because the test was implemented following the 24-month time point after input from the FDA.

Table 8: IVRT Data for Primary Registration 60-g (b) (4) Batches stored at 25°C/60% RH

Batch	Date of Manufacture	IVRT µg/cm²/min^(0.5)	
		30 months	36 months
C829718	OCT-2017		(b) (4)
C830902	OCT-2017		
C831900	OCT-2017		

IVRT data are presented in tables (9-11) below for the 2-g Aluminum primary registration batches stored at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH. The data indicate that the release rate increases with time and also increases at the accelerated storage temperature condition of 40°C/75% RH.

Table 9: IVRT Data for Primary Registration 2-g Al Batches stored at 25°C/60% RH

Batch	IVRT µg/cm²/min^(0.5)		
	3 months[a]	6 months	9 months
RR6N		(b) (4)	
RR6S			
RR6U			

a. Samples tested at 3 months were stored at 5°C/Ambient RH.

Table 10: IVRT Data for Primary Registration 2-g Al Batches stored at 30°C/75% RH

Batch	IVRT µg/cm²/min^(0.5)		
	3 months	6 months	9 months
RR6N		(b) (4)	
RR6S			
RR6U			

Table 11: IVRT Data for Primary Registration 2-g Al Batches stored at 40°C/75% RH

Batch	IVRT µg/cm²/min^(0.5)	
	3 months	6 months
RR6N		(b) (4)
RR6S		
RR6U		

Since there is an increase in the in vitro drug release during stability as the product ages as well as under accelerated storage condition based on the provided IVRT data, the Applicant was asked (IR2.1 in Appendix 1) to provide root cause analysis of this increase and to provide scientific justification that the increase in drug release during stability/storage will not impact the in vivo release and/or in vivo performance of the drug product (both local and systemic). In response, the Applicant noted that no root cause has been identified for the increase in the in vitro release of tapinarof from tapinarof cream, 1% as the product ages or is stored at accelerated conditions. The physical properties of tapinarof cream, 1% including apparent viscosity, (b) (4) globule size (b) (4),

and tapinarof crystallization were not changed when stored at the long-term storage condition of 25°C.

The Applicant noted that it is possible that the IVRT method is sensitive to small changes in the microstructure of the cream ((b) (4) emulsion). The IVRT method used a synthetic Nylon 0.45µm membrane and the composition of the receiving solvent (60:20:20) Dimethyl sulfoxide (DMSO)/isopropanol/water is used due to the low aqueous solubility of tapinarof. This strong solvent is used to force diffusion of tapinarof from the cream through the synthetic membrane into the organic solvent. The microstructure of the cream is disrupted at the filter membrane surface by the strong solvent as tapinarof diffuses into the receiving solvent.

The Applicant provided in vitro skin penetration (IVPT) data on 3 freshly prepared batches compared to one batch that was stored at 25°C/60%RH and 30°C/75%RH for 36 months. Only one fresh Batch (AG7A) showed a statistically significant higher amount of tapinarof delivered in the receptor solution in 24 hours compared to the batch C829718 stored over 36 months at 25°C/60% RH and 30°C/75% RH. Batch C829718 stored for 36 months at 30°C/75% RH showed a statistically significantly higher amount of tapinarof in the epidermis as compared to one fresh batch (AG6Y) but was not statistically significantly different from any other batches. The Applicant did not report the integrity of the skin (IVPT study) or membrane (IVRT study), however, that may have resulted in increased permeation/release of the drug. No correlation could be made between tapinarof penetration and the observed increase in IVRT profiles on storage.

The Applicant also provided PK data from pivotal clinical studies and noted that four different batches of drug product were used during the Phase 3 program and the age of batches at time of clinical use ranged between 6 months and 36 months. Tapinarof concentrations in plasma were mostly undetectable throughout the trials with 95% of samples below quantifiable limits (BQL, <50 pg/mL) in study DMVT-505-3001 and 98% of samples BQL (<50 pg/mL) in study DMVT-505-3002. There were only 13/395 samples with measurable concentrations across the 2 studies. The highest observed concentration was 418 pg/mL. Plasma samples were mostly undetectable throughout the study, regardless of lot number used or time of enrollment. The Applicant also noted that the consistency, robustness, and predictability of the clinical data from the Phase 3 program further support the lack of an in vivo effect from increased drug release during stability/storage. Office of Clinical Pharmacology (OCP) confirmed (via email on 01/05/2022) that based on the limited data from the Phase 3 trials which used a wider age range of the formulation, there does not appear to be any effect of the age of the formulation on the degree of systemic exposure. In the maximum use study, the sponsor used formulation with age ranging between 30 to 35 months which is rather narrow to make any conclusions.

Since there are no apparent concerns on the in vivo performance of the drug product from an increased in vitro drug release during stability, the Applicant's proposed IVRT acceptance criteria are acceptable.

The Applicant has been requested to do IVR testing along with other critical quality attributes on first three commercial lots throughout the stability period in an IR (below) dated Oct. 29, 2021 sent by DP reviewer which the Applicant has agreed.

Initiate stability studies on first three commercial lots (60-g pack) as per ICH Q1A (R2) and include stability study protocol for periodic monitoring of all critical quality attributes, including the globule size measurement, IVRT, and for the absence of Burkholderia cepacia complex (per USP <60>) and report the test result in the Annual Report.

3. Formulation bridging

The formulation development history of tapinarof cream is provided in the link below:
\\CDSESUB1\evsprod\nda215272\0001\m2\27-clin-sum\summary-biopharma.pdf
The formulation used in the pivotal clinical studies (formulation F) is same as the proposed commercial formulation. No in vitro or in vivo formulation bridging study is needed.

Appendix 1

List of Deficiencies communicated to the Applicant during review cycle

Information Request 1 (IR1)

The following deficiency was conveyed to the Applicant in the 74-day letter.

1. Provide IVRT data and profiles for clinical and registration batch(es) at release and stability in electronic format (e.g. MS Excel) as described below:
Chamber ID: # (identify each cell assignment)
Sample volume removed: mL
Diffusion cell area: cm^2

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					

Reviewer's comments:

The Applicant provided the raw data as requested which can be found in the link below.
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\\CDSESUB1\evsprod\nda215272\0004\m3\32-body-data\32r-reg-info\32r4-ivrt_clin_prim_stabil_raw_data.xlsx

Information Request 2 (IR2)

1. Your provided IVRT data shows that there is an increase in drug release during stability as the product ages as well as under accelerated storage conditions. Provide the root cause of this increase in drug release. Also provide scientific justification that the increase in drug release during stability/storage will not impact the in vivo release and/or in vivo performance of the drug product (both local and systemic).

Reviewer's comments:
The Applicant responded to the above IR and the response is provided in the link below. It has been discussed in the relevant sections above.
\\CDSESUB1\evsprod\nda215272\0013\m1\us\m1-11-4-multiple-module-information-amendment.pdf

Information Request 3 (IR3)

1. Provide a tabular listing of the respective batch numbers and age of the drug products (i.e., how many months since it was manufactured) used in all PK (including MUST), and pivotal clinical trials along with clinical trial numbers. If this information has been provided already in the NDA submission, provide the location of this information.

Reviewer's comments:

The Applicant responded to the above IR and the response is provided in the link below.

\\CDSESUB1\evsprod\nda215272\0015\m1\us\m1-11-1-quality-information-amendment.pdf

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.

***Secondary Reviewer Name*:** Tapash Ghosh, Ph.D.

Kalpana Paudel

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215272
Assessment Cycle Number	01
Drug Product Name/ Strength	Tapinarof cream 1%
Route of Administration	Topical (dermal)
Applicant Name	Dermavant Sciences, Inc.
Therapeutic Classification/ OND Division	Psoriasis Agents (4029050)/ CDER/OND/OII/DDD
Manufacturing Site	Glaxo Operations UK Ltd [redacted (b) (4)]
Method of Sterilization	Non-sterile drug product

Assessment Recommendation: **Adequate**

Assessment Summary: The drug product is a non-sterile, [redacted (b) (4)], topical cream, packaged in a multidose 60 g tube (commercial pack) or 2 g tube (physician sample). The critical aspects from the microbiology perspective are microbiological release testing and [redacted (b) (4)]. These aspects were reviewed and deemed acceptable. The applicant has provided sufficient data to support the microbial limits method suitability for TAMC and TYMC as per USP <61>, *S. aureus* and *P. aeruginosa* as per USP <62>, and BCC as per USP <60>. The applicant has also provided sufficient data to support the [redacted (b) (4)] listed in the stability specification and within the required pH range. Based on the information submitted, there are no deficiencies identified. The application is recommended for approval.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD SN 0001 (SD#1)	05/26/2021
eCTD SN 0004 (SD#4) †	07/28/2021
eCTD SN 0005 (SD#5) †	07/30/2021
eCTD SN 0019 (SD#19) †	12/14/2021
eCTD SN 0022 (SD#22) †	01/26/2022

† Amendment responses to Information Requests (IRs), including Microbiology content.

Highlight Key Issues from Last Cycle and Their Resolution: N/A. This is a first cycle review.

Remarks:

The subject of review is submitted electronically (eCTD). Some tables in this review are excerpted from the electronic submission. All references to Module, Section, and pdf documents in this review are from the ANDA submission dated 05/26/2021 (SN0001) except where noted otherwise.

An IR was sent to the applicant via email dated 07/21/2021 including 2 microbiology questions from the filing review. The applicant responded to Microbiology Question 2 and Question 1 in the Amendments dated 07/28/2021 (SN0004) and 07/30/2021 (SN0005), respectively. The responses are incorporated into the subject review.

An additional IR was sent by the drug product reviewer to the applicant dated 12/03/2021 to request an in-use stability study including physical, chemical, and microbiology stability data. The latter is addressed in this review.

An additional IR was sent to the applicant dated 01/21/2022 to clarify the microbial limits testing approach as described in 3.2.P.3.2. The response is incorporated in this review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents: NDA 215272 microbiology filing review, N215272 filing review.pdf, 07/15/2021, by L. Ashmore - Two product quality microbiology questions.

S DRUG SUBSTANCE

(SN0001, 3.2.S.4.1, specification.pdf, p. 1 of 1; 3.2.P.2, pharmaceutical-development.pdf, p. 113 of 114); 3.2.S.4.5, justification-of-specification.pdf, p. 4 of 4)

The drug substance is supplied non-sterile. The drug substance does not have a microbial limit specification (3.2.S.4.1); a justification is provided (3.2.S.4.5, p. 4 of 4). The water activity in the tapinarof drug substance is low (typically <0.1%), such that the drug substance does not support microbial growth. Microbial limits testing on primary stability batches met the criteria for USP <61> with TAMC and TYMC of < (b) (4) CFU/g, and the water activity was below 0.6 (i.e., the amount specified for microbial growth in USP <1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products).

Assessment: ***Adequate***

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**

(SN0001, 2.3.1, introduction.pdf, pp. 1-2 of 2; 3.2.P.1, description-and-composition.pdf, p. 1 of 1; 3.2.P.2, pharmaceutical-development.pdf, p. 113 of 114)

The drug product is a white to off-white, [redacted] emulsion cream, prepared at a 1% concentration, [redacted] and supplied in a multidose 60 g tube (commercial product) or a 2 g tube (physician's sample). The drug product is administered topically for plaque psoriasis.

- **Drug product composition –**

(SN0001, 3.2.P.1, description-and-composition.pdf, p. 1 of 1; 2.3.P, drug-product-dmvt-505(tapinarof)-cream.pdf, pp. 5, 17 of 40)

Tapinarof Cream, 1%

Ingredient	Quantity (% w/w)	Function	Reference to Standard
Tapinarof	1.00	Active pharmaceutical ingredient	In House (Dermavant)
Water, Purified [a]	[redacted]		USP-NF
Sodium Citrate Dihydrate			USP-NF
Disodium Edetate			USP-NF
Citric Acid Monohydrate			USP-NF
Medium Chain Triglycerides			USP-NF
Propylene Glycol			USP-NF
Emulsifying Wax			USP-NF
Diethylene Glycol Monoethyl Ether			USP-NF
Polyoxyl 2 Stearyl Ether			USP-NF
Polysorbate 80			USP-NF
Polyoxyl 20 Stearyl Ether			USP-NF
Benzoic Acid			USP-NF
Butylated Hydroxytoluene			USP-NF

[a] The purified water [redacted]

None of the excipients is of human or animal origin (2.3.P, p. 17 of 40).

- **Description of container closure system –**

(SN0001, 2.3.1, introduction.pdf, p. 1 of 2; 2.3.P, drug-product-dmvt-505(tapinarof)-cream.pdf, p. 5 of 40; 3.2.P.7, container-closure-systems.pdf, pp. 1-9 of)

Commercial: 60-g [redacted] laminate [redacted] tube with a [redacted] shoulder, a peelable sealed membrane, and white [redacted] cap
Manufacturer: [redacted]

Physician sample: 2-g aluminum (Al) tube with sealed membrane and membrane piercing white (b) (4) cap
Manufacturer: (b) (4)

The tubes and caps are (b) (4) .

Assessment: ***Adequate***

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Lisa Ashmore (Shelton)

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Julie Nemecek

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Nina Ni

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