CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215272
PDUFA Goal Date	May 26, 2022
OSE RCM #	2021-1181
Reviewer Name(s)	Carla Darling, PharmD, BCPS
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Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	May 19, 2022
Subject	Evaluation of Need for a REMS
Established Name	Tapinarof
Trade Name	Vtama
Name of Applicant	Dermavant Sciences GMBH
Therapeutic Class	Aryl hydrocarbon receptor (AhR) modulating agonist
Formulation	Cream 1%
Dosing Regimen	Apply a thin layer to affected area(s) once daily

[a] Carlisha Gentles contributed to this review but was no longer in the Division of Risk Management when the review was completed.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vtama (tapinarof) is necessary to ensure the benefits outweigh its risks. Dermavant Sciences GMBH (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 215272 for tapinarof with the proposed indication for the topical treatment of plaque psoriasis in adults. The Applicant did not submit a proposed REMS or risk management plan with this application. The clinical reviewer concluded that tapinarof was effective in treating patient with plaque psoriasis.

The Division of Risk Management (DRM) and the Division of Dermatology and Dentistry (DDD) agree that a REMS is not necessary to ensure the benefits of tapinarof outweigh its risks. The benefit for the treatment of plaque psoriasis was demonstrated as tapinarof resulted in a statistically significant proportion of patients achieving a Physician's Global Assessment (PGA) scores of 0 ("clear") or 1 ("almost clear") with a ≥2-point decrease from baseline compared to vehicle in the pivotal, vehicle-controlled phase 3 trials. The risks associated with tapinarof include folliculitis, contact dermatitis and headaches. These risks are not included in (b) (4) of draft labeling. Likely prescribers of tapinarof should be familiar with monitoring and management of these risks. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Vtama (tapinarof) is necessary to ensure the benefits outweigh its risks. Dermavant Sciences, Inc. submitted a New Drug Application (NDA) 215272 for tapinarof with the proposed indication for the treatment of plaque psoriasis (PSO) in adults. The Applicant did not submit a proposed REMS or risk management plan with this application. This application is under review in the Division of Dermatology and Dentistry.

2. Background

2.1. Product Information

Vtama (tapinarof), a new molecular entity (NME)[b], is an aryl hydrocarbon receptor (AhR) modulating agonist proposed for the treatment of PSO. The specific mechanism of action in PSO is unknown. However, the Applicant proposes that by specifically binding to and activate AhR, tapinarof has the potential to downregulate pro-inflammatory cytokines and regulate skin barrier protein expression thereby reducing inflammation associated with PSO.[1] Tapinarof 1% cream is a topical treatment that is

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

intended for long-term disease management[c] of plaque psoriasis in adults. The proposed dosage regimen is to apply a thin layer to the affected area(s) once daily. Tapinarof is intended for administration by patients or caregivers in the outpatient setting. If approved, tapinarof will be the first drug in the pharmacological class of AhR modulating agonists.[2]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215272 relevant to this review:

- 05/26/2021: NDA 215272 submission for the treatment of plaque psoriasis in adults received
- 11/10/2021: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tapinarof.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations.[3] The pathophysiology is complex and involves several cellular components and cytokines of the immune system.[3] Psoriasis affects about 3% of the United States population.[4,d] It can begin at any age, however, one population study of the age of onset revealed two peaks, around ages 30-39 and at ages 50-69.[5] Plaque psoriasis is the most common form and accounts for about 85-90% of cases.[6] It is characterized by well-demarcated, erythematous plaques with overlying coarse scale that typically affect the scalp, extensor elbows, knees and gluteal cleft.[3] Psoriasis is associated with comorbid conditions that include psoriatic arthritis, eye disorders, and other disorders such as depression/suicide, cardiovascular disease, and metabolic syndrome.[3] Plaque psoriasis has a substantial impact on patient quality of life. In addition to the physical manifestations, patients also report significant social and psychologic effects such as limitations on activities, depression, anxiety, embarrassment and stigma, and social discrimination.[7] Psoriasis is also associated with increased overall mortality.[e] Some deaths may be due to adverse effects from systemic therapies; however, psoriasis-related mortality may also be related to the risk of comorbid cardiovascular disease.[3]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

3.2. Description of Current Treatment Options

Multiple products are approved for the treatment of adults with moderate-to-severe plaque psoriasis. None of these treatments provide a permanent cure and all are associated with one or more serious risks. Development of additional therapeutic options continues to be important due to variability in effectiveness and tolerability, as well as uncertainty regarding long-term effects.

Currently approved drugs for the treatment of plaque psoriasis in adults with varying degrees of severity of the condition include: topical steroids, such as betamethasone dipropionate and halobetasol propionate; topical agents, plant-based solution, calcipotriene/betamethasone (vitamin-D analog plus corticosteroid), tazarotene (receptor-selective retinoid); methotrexate; tumor necrosis factor (TNF) inhibitors, etanercept, adalimumab, certolizumab pegol, and infliximab; IL-12 and IL-23 antagonist ustekinumab; IL-17A antagonists secukinumab and ixekizumab; IL-17A receptor antagonist brodalumab; IL-23 antagonists, guselkumab, tildrakizumab, and risankizumab; T-cell inhibitor cyclosporine (CSA); retinoid acitretin; and phosphodiesterase-4 (PDE-4) inhibitor apremilast. Phototherapy, with either PUVA (UVA light combine with the photosensitizer, psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for patients with moderate to severe plaque psoriasis. Phototherapy requires frequent office visits and carries an increased risk of squamous cell carcinoma of the skin.[3]

Usage of corticosteroids may lead to pruritus, thinning of the skin, and erythema. Vitamin-D analogs usage is associated with burning, folliculitis, and worsening psoriasis. Patients using tazarotene may experience application site irritation and blistered skin. Plant-based solutions are associated with hair loss, pruritus, skin thinning and erythema.[8] There are 11 FDA approved biologic therapies for plaque psoriasis, please refer to Table 1 in Appendix 10.2 for list of these products, associated risks and risk management strategies.

Currently, Siliq (brodalumab) is the only biologic approved for moderate to severe plaque psoriasis that has a REMS. The goal of the Siliq REMS is to mitigate the observed risk of suicidal ideation and behavior (SIB) including completed suicides, by ensuring that prescribers are educated about the risk of SIB with brodalumab therapy, counsel patients about this risk of SIB and the need to seek medical attention for manifestations of SIB, new onset or worsening depression, or other mood changes.

REMS were previously approved for the TNF inhibitors (etanercept, adalimumab, certolizumab pegol, and infliximab) and Stelara (ustekinumab). These REMS consisted of a Medication Guide and communication plan (CP) to address serious risks (see Appendix 10.2 for Table 1). The TNF inhibitors were released from REMS requirements in 2011 and ustekinumab was released in 2017 because the CP activities were completed, and the REMS assessments demonstrated that the REMS goals were being met. Medication Guides remain part of the labeling for these agents.

4. Benefit Assessment

The efficacy and safety of tapinarof for the treatment of plaque psoriasis in adults is supported by two identical phase 3, pivotal trials, Study 3001 (NCT03956355) and Study 3002 (NCT03983980). Additional supportive evidence came from a phase 3 open-label long-term safety trial, Study 3003 (NCT04053387).

Both studies were multicentered, randomized, double-blind, and vehicle-controlled to evaluate the efficacy and safety of tapinarof in adults with plaque psoriasis. A total of 1025 patients were randomized 2:1 to receive tapinarof cream or vehicle cream once daily for 12 weeks. The primary efficacy endpoint of the studies was the proportion of patients that achieved treatment success, defined as a Physician's Global Assessment (PGA) score of "clear" (0) or "almost clear" (1) and at least a 2-grade improvement from baseline at week 12. Baseline disease severity was graded using the 5-point PGA. The majority of patients had "Moderate" disease (82%), while 10% had "Mild" disease, and 8% had "Severe" disease at baseline.[9]

Results:

The review team determined the primary efficacy data to support approval of tapinarof was demonstrated in the pivotal studies, Study 3001 and 3002. Tapinarof was statistically superior to the vehicle in both trials (p-values < 0.001). Table 1 highlights the results of the primary endpoints for Study 3001 and Study 3002.

Table 1: Results of the Primary Efficacy Endpoint*

	Study 3001		Study 3002	
	Tapinarof (N=340)	Vehicle (N=170)	Tapinarof (N=343)	Vehicle (N=172)
PGA Response at Week 12				
Proportion	36%	6%	40%	6%
Difference (95% CI)[3]	29% (23%, 36%)		34% (27%, 41%)	
Relative Risk (95% CI)[4]	5.8 (2.9, 11.6)		6.1 (3.3, 11.4)	
P-value[4]	<0.001		<0.001	

*Modified from Statistical and Clinical Evaluation Section of Multi-disciplinary Review as of May 4, 2022

The clinical reviewer concluded that tapinarof has provided reliable and statistically significant evidence that tapinarof can help patients achieve improvements with their psoriasis.[7,f]

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

The safety database for tapinarof is comprised of 683 patients from two phase 3 studies (Study 3001 and Study 3002) and one long-term extension study (Study 3003) with 763 participants. The most commonly reported adverse events[g] (AEs) ≥ 1% of participants receiving tapinarof in the safety database were folliculitis (20%), nasopharyngitis (11%), contact dermatitis (7%), headache (4%), pruritus (3%), and influenza (2%).[9]

Folliculitis, contact dermatitis and headache were identified by the Applicant as Adverse Events of Special Interest (AESIs).[10] Folliculitis was observed more frequently in the tapinarof-treatment group (20%) than the vehicle group (1%)[9]. Most folliculitis events were assessed as Grade 1 or 2 in intensity.[7] Drug discontinuation due to folliculitis was low throughout the development program, occurring in 2.8% of patients in the tapinarof-treatment group and 0% of patients in the vehicle group.[7] Contact dermatitis was reported more frequently in the tapinarof-treatment group (7%) than the vehicle group (1%).[9] Most contact dermatitis events assessed as Grade 1 or 2 in intensity.[7] Drug discontinuation due to contact dermatitis was low across the development program with 2.9% of patients in the tapinarof-treatment group and 0% of patients in the vehicle group.[7] Headaches were reported as 4% in the tapinarof-treatment group and 1% in the vehicle group.[9] Most events were assessed as Grade 1 or 2 in intensity.[7] Drug discontinuation due to headaches was uncommon in the clinical studies with an incidence rate of 0.4% of patients in the tapinarof-treatment group and 0% of patients in the vehicle group.[7] Most of the AESIs were mild, localized reactions commonly observed among other topical agents to treat plaque psoriasis and managed by dermatologists.

Deaths

One death occurred in the clinical development program during the long-term extension study (Study 3003). The reported death was due to a myocardial infarction in a 73-year-old male with a medical history of cardiovascular disease. The death was not considered treatment related per the clinical reviewer.[7]

6. Expected Postmarket Use

Tapinarof is likely to be prescribed by dermatologists and is expected to primarily by used by patients in the outpatient setting. If approved, tapinarof will be the first aryl hydrocarbon receptor modulating agonist; however, several approved topical agents for the treatment of plaque psoriasis have a similar risk profile and healthcare providers who are likely to prescribe tapinarof should be familiar with the risks.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or any risk management activities for tapinarof.

8. Discussion of Need for a REMS

Tapinarof is an Aryl hydrocarbon receptor (AhR) modulating agonist proposed for the treatment of plaque psoriasis. Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations associated with significant social and psychologic effects and increased overall mortality. Use of tapinarof will provide an option for patients who are unable to receive, tolerate or adequately benefit from currently available therapies.

The Clinical Reviewer recommends approval of tapinarof on the basis of the efficacy and safety information currently available.[7] The pivotal studies, Study 3001 and Study 3002, support the efficacy of tapinarof as evidenced by a statistically significant improvement in the proportion of patients who achieved PGA scores of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline (p-values < 0.001) with an acceptable safety profile.

Tapinarof is associated with a risk of folliculitis, contact dermatitis, and headaches. None of the events were serious and only a very small percentage led to discontinuations. As these risks of folliculitis, contact dermatitis, and headaches do not pose any serious safety risks, this reviewer concluded that based on the available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

The clinical reviewer has determined that the benefit/risk assessment for tapinarof supports approval.

Based on the available data, the benefit-risk profile is favorable and a REMS is not necessary for tapinarof to ensure the benefits outweigh the risks. At the time of this review, labeling discussions were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Dermavant. Clinical Overview for Tapinarof. *NDA 215272.* May 26, 2021.
2. Bissonnette R, Gold L, Rubenstein D, Tallman A, Armstrong A. Tapinarof in the treatment of psoriasis: A review of the unique mechanism of action of a novel therapeutic aryl hydrocarbon receptor–modulating agent. *Neurology.* 2021;84(4):1059-1067.
3. Feldman S. Psoriasis: Epidemiology, clinical manifestations, and diagnosis. In: Dellavale RP CD, K, and Ofori, AO, ed. *UptoDate.* Walham, MA UptoDate; 2021.
4. Rachakonda T, Schupp, CW, Armstrong, AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.

5. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *Journal of Investigative Dermatology.* 2013;133(2):377-385.
6. Nestle F, Kaplan, DH, Barker, J. Psoriasis. *NEJM.* 2009;361(5):496- 509.
7. Division of Dermatology and Dentistry. Multi-Discplinary Review and Evaluation for Tapinarof. *NDA 215272.* 2022.
8. Xu S, Zhang X, Pan M, Shuai Z, Xu S, Pan F. Treatment of plaque psoriasis with IL-23p19 blockers: A systematic review and meta-analysis. *International immunopharmacology.* 2019;75:105841.
9. Dermavant. DRAFT Vtama (tapinarof) Prescribing Information. *NDA 215272.* April 4, 2022.
10. Dermavant. Summary of Clinical Safety of Tapinarof. *NDA 215272.* May 26, 2021.
11. Enbrel (etanercept) Prescribing Information. Thousand Oaks, CA: Amgen; 08/2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103795s5582lbl.pdf. Accessed May 4, 2022.
12. Siliq (brodalumab) Prescribing Information. *BLA 761032.* Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 02/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf. Accessed May 4, 2022.
13. Taltz (ixekizumab) Prescribing Information. *BLA 125521.* Indianapolis, IN: Eli Lilly and Company; 03/2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125521s014lbl.pdf. Accessed May 4, 2022.
14. Cosentyx (secukinumab) Prescribing information. *BLA 125504.* East Hanover, NJ: Novartis Pharmaceuticals Corporation; 12/2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125504_S050_S051lbl.pdf. Accessed May 4, 2022.
15. Stelara (ustekinumab) Prescribing Information. *BLA 761044.* Horsham, PA: Janssen Biotech, Inc.; 12/2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761044s008lbl.pdf. Accessed May 4, 2022.
16. Cimzia (certolizumab pegol) Prescribing Information. *BLA 125160.* Smyrna, GA: UCB, Inc.; 09/2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125160s293lbl.pdf. Accessed May 4, 2022.
17. Humira (adalimumab) Prescribing Information. *BLA 125057.* North Chicago, IL: AbbVie Inc.; 02/2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf. Accessed May 4, 2022.
18. Remicade (infliximab) Prescribing Information. *BLA 103772.* Horsham, PA: Janssen Biotech, Inc.; 10/2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103772s5401lbl.pdf. Accessed May 4, 2022.
19. Skyrizi (risankizumag-rzaa) Prescribing Information. *BLA 761105.* North Chicago, IL: AbbVie Inc.; 01/2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761105s014lbl.pdf. Accessed May 4, 2022.
20. Ilumya (tildrakizumab-asmn) Prescribing Information. *BLA 761067.* County Carlow, Ireland: Merck and Dohme Corporation; 03/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761067s000lbl.pdf. Accessed May 4, 2022.
21. Tremfya (guselkumab) Prescribing Information. *BLA 761061.* Horsham, PA: Janssen Biotech, Inc.; 07/2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761061s007lbl.pdf. Accessed May 4, 2022.

10.2. Table 1. Biologic Therapies Approved for Plaque Psoriasis

Biologic Therapies Approved in the US for Plaque Psoriasis[11-21]

Name (Generic), Approval Year *Drug class*	Route	Safety issues	Risk Management Approaches: Current REMS, Boxed Warning, Medication guide
Enbrel (etanercept), 1998 *TNF inhibitor*	Injection, subcutaneous	Serious infections, malignancies, invasive fungal infections, neurologic reactions, heart failure, hematologic reactions, allergic reactions, autoimmunity	• Boxed Warning for serious infections and malignancies • Medication Guide
Remicade (infliximab), 1999 *TNF inhibitor*	Injection, intravenous infusion	Serious infections, invasive fungal infections, malignancies, hepatitis B virus reactivation, hepatoxicity, heart failure, cytopenias, hypersensitivity, cardiovascular and cerebrovascular reactions, demyelinating disease, lupus-like syndrome	• Boxed Warning for serious infections and malignancy • Medication Guide
Humira (adalimumab) 2002 *TNF inhibitor*	Injection, subcutaneous	Serious infections, invasive fungal infections, malignancies, anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, lupus-like syndrome	• Boxed Warning for serious infections and malignancy • Medication Guide
Cimzia (certolizumab) 2008 o *TNF inhibitor*	Injection, subcutaneous	Serious infections, malignancies, heart failure, hypersensitivity reactions, hepatitis B virus reactivation, neurologic reactions, hematological reactions, autoimmunity	• Boxed Warning for serious infections and malignancy • Medication Guide

Stelara (ustekinumab) 2009 *IL-12 and IL-23 antagonist*	Injection, subcutaneous p	Infections, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy, noninfectious pneumonia	• Medication Guide
Cosentyx (secukinumab), 2015 *Anti-IL-17A antibody*	Injection, subcutaneous	Infections, inflammatory bowel disease, hypersensitivity reactions	• Medication Guide
Taltz (ixekizumab) 2016 *Anti-IL-17A*	Injection, subcutaneous	Infections, hypersensitivity, inflammatory bowel disease	• Medication Guide
Siliq (brodalumab) 2017 *IL-17A receptor antagonist*	Injection, subcutaneous	Suicidal ideation and behavior, infections, Crohn's disease	• REMS with ETASU for the risk of suicidal ideation and behavior (SIB) • Boxed Warning for SIB • Medication Guide
Tremfya (guselkumab), 2017 *Interleukin 23 Antagonist*	Injection, subcutaneous	Hypersensitivity, infections	• Medication Guide
Ilumya (tildrakizumab), 2018 *Interleukin 23 Antagonist*	Injection, subcutaneous	Hypersensitivity, infections	• Medication Guide
Skyrizi (risankizumab) 2019 *Interleukin 23 Antagonist*	Injection, subcutaneous	Infections	• Medication Guide

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